Clinical Trial Protocol

	Document Number:	**c26441921-04**
EudraCT No.	2018-004806-24	
BI Trial No.	1346-0029	
BI Investigational Medicinal Product	BI 425809	
Title	A study to investigate the effects of donepezil on the pharmacokinetics of BI 425809 and vice versa in healthy male and female subjects (Open-label, two-treatment, two-period, one fixed sequence cross-over design)	
Lay Title	A study in healthy men and women to test which effects donepezil 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 3))	
Version and Date	Version: 4.0	Date: 29 May 2019

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	28 January 2019
Revision date	29 May 2019
BI trial number	1346-0029
Title of trial	A study to investigate the effects of donepezil on the pharmacokinetics of BI 425809 and vice versa in healthy male and female subjects (Open-label, two-treatment, two-period, one fixed sequence cross-over design)
Principal Investigator:	
Trial site	
Clinical phase	I
Trial rationale	Donepezil is a common medication used in patients diagnosed with Alzheimer's Disease (AD). As BI 425809 is developed as a symptomatic treatment for AD it is very likely that it may be used on top of donepezil in clinical practice. Therefore it is crucial to investigate if there are any interactions between BI 425809 and donepezil when administered together before their concomitant use will be allowed in Phase 3 trials and later in clinical practice
Trial objectives	*Part 1:* To investigate the effect of co-administration of multiple doses of donepezil on the single-dose pharmacokinetics of BI 425809 in healthy subjects *Part 2:* To investigate the effect of co-administration of multiple doses of BI 425809 on the single-dose pharmacokinetics of donepezil in healthy subjects
Trial design	*Part 1 + 2:* Open-label, two-treatment, two-period, one fixed sequence cross-over design
Trial endpoints:	*Primary endpoints:* • Part 1: $AUC_{0-\infty}$ and C_{max} of BI 425809 • Part 2: $AUC_{0-\infty}$ and C_{max} donepezil *Secondary endpoints:* • Part 1: AUC_{0-tz} of BI 425809 • Part 2: AUC_{0-tz} of donepezil
Number of subjects **total entered** **each treatment**	 N = 32 Part 1: N = 18 Part 2: N = 14
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:	BI 425809, film-coated tablet
Strength:	25 mg
Mode of admin.:	Oral with 240 mL of water
Trial product 2:	Donepezil-HCl-ratiopharm® 5 mg, film-coated tablets
Strength:	5 mg
Mode of admin.:	Oral administration with 240 mL of water. Donepezil dosing follows an up-titration regime from 5 mg to 10 mg for tolerability reasons.
Duration of treatment	Part 1*: *Treatment A (Reference 1):* Trial product 1: single dose of 25 mg BI 425809 on Day 1, Visit 2 *Treatment B (Test 1):* Trial product 1: single dose of 25 mg BI 425809 on Day 22, Visit 3 Trial product 2: multiple doses of 5 mg donepezil q.d. on Days 1-7, Visit 3 multiple doses of 10 mg donepezil q.d. on Days 8-28, Visit 3 *There will be no wash-out period between treatment A and B. Part 2**: *Treatment C (Reference 2):* Trial product 2: single dose of 10 mg donepezil on Day 1, Visit 2 *Treatment D (Test 2):* Trial product 2: single dose of 10 mg donepezil on Day 10, Visit 3 Trial product 1: multiple doses of 25 mg BI 425809 q.d. on Days 1-24, Visit 3 **There will be no wash-out period between treatment C and D
Statistical methods	The effects of donepezil on the pharmacokinetics of BI 425809 (Part 1) and the effects of BI 425809 on the pharmacokinetics of donepezil (Part 2) will be evaluated based on the point estimates of the intra-subject ratio (test to reference treatment) 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-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range was not specified. The statistical model will be a (mixed effects) ANOVA on the log-transformed parameters, including effects for 'subjects' and 'treatment'. CIs will be calculated based on the residual error from ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Part 1

Visit*	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	$PK_{plasma\ (BI\ 425809)}$	$PK_{plasma\ Donepezil}$	Safety assessments	12-lead ECG[14]	Vital signs (BP, PR)[14]	Questioning for AEs and concomitant therapy[6]
1	-21 to -1	n.a.	n.a.	Screening[1]	x[10]			x[12,13]	x	x	
2 (Treatment A)	-3 to -1	-24:00	n.a.		x[9]						x
	1	-10:00	08:00	Admission to trial site	x[15]				x	x	x[7]
		00:00	18:00	**Drug administration, 25 mg BI 425809**		x[2]					
		00:30	18:30			x					
		01:00	19:00			x					
		02:00	20:00	240ml fluid intake		x					
		03:00	21:00			x					
		03:30	21:30			x					
		04:00	22:00	240 mL fluid intake, Dinner, thereafter start of bed rest[16]		x			x	x	x
		04:30	22:30			x					
		05:00	23:00			x					
	2	06:00	00:00			x					
		08:00	02:00			x					
		10:00	04:00			x					
		12:00	06:00	End of bed rest[16], Breakfast[3]		x			x	x	x
		24:00	18:00			x					x
	3	34:00	04:00			x					x
		38:00	08:00	Discharge[11]					x	x	x
		48:00	18:00	Ambulatory visit		x					x
	4	72:00	18:00	Ambulatory visit		x					x
	5	96:00	18:00	Ambulatory visit	x	x					x
	6	120:00	18:00	Ambulatory visit		x					x
	7	144:00	18:00	Ambulatory visit		x					x
	8	168:00	18:00	Ambulatory visit	x[10]	x					x
3 (Treatment B)	1	-02:00	16:00	Admission to trial site	x[15]						x
		00:00	18:00	Admin. 5 mg donepezil			x[2]		x[2]	x[2]	x[2,7]
	2	14:00	08:00	Discharge[11]					x	x	x
		24:00	18:00	Ambulatory visit[11], admin. 5 mg donepezil					x[2]	x[2]	x[2,7]
	3	48:00	18:00	Ambulatory visit[11], admin. 5 mg donepezil							x[2,7]
	4	72:00	18:00	Ambulatory visit[11], admin. 5 mg donepezil	x[10]				x[2]	x[2]	x[2,7]
	5	96:00	18:00	Ambulatory visit[11], admin. 5 mg donepezil							x[2,7]
	6	120:00	18:00	Ambulatory visit[11], admin. 5 mg donepezil					x[2]	x[2]	x[2,7]
	7	144:00	18:00	Ambulatory visit[11], admin. 5 mg donepezil			x[8]				x[2,7]
	8	168:00	18:00	Ambulatory visit[11], admin. 10 mg donepezil	x[10]			x[12]	x[2]	x[2]	x[2,7]
	9	192:00	18:00	Ambulatory visit[11], admin. 10 mg donepezil							x[2,7]
	10	216:00	18:00	Ambulatory visit[11], admin. 10 mg donepezil							x[2,7]
	11	240:00	18:00	Ambulatory visit[11], admin. 10 mg donepezil							x[2,7]
	12	264:00	18:00	Ambulatory visit[11], admin. 10 mg donepezil	x[10]				x[2]	x[2]	x[2,7]
	13	288:00	18:00	Ambulatory visit[11], admin. 10 mg donepezil							x[2,7]
	14	312:00	18:00	Ambulatory visit[11], admin. 10 mg donepezil			x[8]				x[2,7]

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	$PK_{plasma\ (BI\ 425809)}$	$PK_{plasma\ Donepezil)}$	Safety assessments	12-lead ECG[14]	Vital signs (BP, PR)[14]	Questioning for AEs and concomitant therapy [6]
3 (Treatment B)	15	336:00	18:00	Ambulatory visit[11], admin. 10 mg donepezil							x[2,7]
	16	360:00	18:00	Ambulatory visit[11], admin. 10 mg donepezil	x[10]			x[12]	x[2]	x[2]	x[2,7]
	17	384:00	18:00	Ambulatory visit[11], admin. 10 mg donepezil							x[2,7]
	18	408:00	18:00	Ambulatory visit[11], admin. 10 mg donepezil							x[2,7]
	19	432:00	18:00	Ambulatory visit[11], admin. 10 mg donepezil	x[10]		x[8]		x[2]	x[2]	x[2,7]
	20	456:00	18:00	Ambulatory visit[11], admin. 10 mg donepezil			x[8]				x[2,7]
	21	480:00	18:00	Ambulatory visit[11], admin. 10 mg donepezil			x[8]				x[2,7]
	22	494:00	08:00	Admission to trial site	x[5,10]			x[12]	x	x	x[2,7]
		504:00	18:00	**Drug administration, 25 mg BI 425809 + 10 mg donepezil**		x[8]	x[8]				x[2,7]
		504:30	18:30			x					
		505:00	19:00			x					
		506:00	20:00	240 ml fluid intake		x					
		507:00	21:00			x					
		507:30	21:30			x					
		508:00	22:00	240 mL fluid intake, Dinner, thereafter start of bed rest[16]		x			x	x	x
		508:30	22:30			x					
		509:00	23:00			x					
	23	510:00	00:00			x					
		512:00	02:00			x					
		514:00	04:00			x					
		516:00	06:00	End of bed rest[16], Breakfast[3]		x			x	x	x
		528:00	18:00	Drug administration, 10 mg donepezil		x			x[2]	x[2]	x[2,7]
	24	540:00	06:00			x					x[2,7]
		542:00	08:00	Discharge[11]				x[12]	x	x	x[7]
		552:00	18:00	Ambulatory visit[11], admin. 10 mg donepezil		x[8]					x[2,7]
	25	576:00	18:00	Ambulatory visit[11], admin. 10 mg donepezil	x[10]	x[8]	x[8]		x[2]	x[2]	x[2,7]
	26	600:00	18:00	Ambulatory visit[11], admin. 10 mg donepezil		x[8]					x[2,7]
	27	624:00	18:00	Ambulatory visit[11], admin. 10 mg donepezil		x[8]					x[2,7]
	28	648:00	18:00	Ambulatory visit[11], admin. 10 mg donepezil		x[8]					x[2,7]
	29	672:00	18:00	Ambulatory visit[11]	x[10]	x[8]			x[2]	x[2]	x[2,7]
4	44-49	n.a.	n.a.	End of trial examination[4]	x[10]			x[12,13]	x	x	x

1. Screening includes subject information, informed consent, physical examination including neurological assessment, check of vital signs, visual tests, ECG, safety laboratory (including drug screening, alcohol breath test, urine pregnancy testing in females, and faecal occult blood 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 2 h prior to drug administration.
3. If several actions are indicated at the same time point, the intake of meals will be the last action.
4. End of trial examination includes physical examination including neurological assessment, vital signs, visual tests, ECG, safety laboratory, urine pregnancy testing in females, recording of AEs and concomitant therapies, faecal occult blood test.
5. Including urine drug screening and alcohol breath test and urine pregnancy testing in females
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.
7. Includes questioning for 'restrictions'

8. Pre-dose PK, i.e. within 10 min prior to the next drug administration
9. Safety laboratory to be taken within 3 days prior to first trial drug administration of Visit 2 and 3. All results must be available and be checked by the investigator or his/her designee before trial drug administration. For Visit 3, the safety laboratory of day 8, Visit 2 will be used.
10. Includes immunochemical faecal occult blood (iFOB) test
11. Discharge after confirmation of fitness by the investigator/designee
12. Neurological assessment (i.e. Romberg and Unterberger test, assessment of gait, further tests as needed) to be performed at the time points mentioned in the Flow Chart above and at any times CNS adverse events are reported
13. Colour discrimination, visual acuity testing, Amsler grid test: tests will be performed at screening, EOT and at any time visual adverse events are reported
14. All blood pressure measurements, as well as pulse rate and ECG will be measured after at least 5 minutes of rest in the supine position
15. Only urine drug screening and alcohol breath test and urine pregnancy testing in females
16. Bed rest (except going to the toilet)

* There is no wash-out period between Visit 2 and Visit 3. Day 1 of Visit 3 follows directly after day 8 of Visit 2 but these are different days

Part 2

Visit**	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	$PK_{plasma\ (BI\ 425809)}$	$PK_{plasma\ Donepezil)}$	Safety assessments	12-lead ECG[14]	Vital signs (BP, PR)[14]	Questioning for AEs and concomitant therapy[6]
1	-21 to -1	n.a.	n.a.	Screening [1]	x[5]			x[9,10,13]	x	x	
2 (Treatment C)	-3 to -1	-24:00	n.a.	Ambulatory visit	x[12]						x
	-1	-12:00	20:00	Admission to trial site	x[15]						x
	1	-02:00	06:00		x[2]		x[2]	x[10,2]	x[2]	x[2]	x[2,7]
		00:00	08:00	**Drug administration, 10 mg donepezil**							
		01:00	09:00				x				
		02:00	10:00	240 mL fluid intake			x				
		03:00	11:00				x				
		04:00	12:00	240 mL fluid intake, Lunch[3]			x		x	x	x
		06:00	14:00				x				
		08:00	16:00				x				
		10:00	18:00	Dinner[3]			x				
		12:00	20:00				x		x	x	x
	2	18:00	02:00				x				
		24:00	08:00		x		x		x	x	x
	3	48:00	08:00				x				x
	4	72:00	08:00		x		x				x
		72:30	08:30	Discharge[11]				x[10]	x	x	x
	5	96:00	08:00	Ambulatory visit			x		x	x	x
	6	120:00	08:00	Ambulatory visit			x				x
	7	144:00	08:00	Ambulatory visit			x				x
	8	168:00	08:00	Ambulatory visit			x				x
	9	192:00	08:00	Ambulatory visit			x				x
	10	216:00	08:00	Ambulatory visit	x		x	x[10]	x	x	x
	11	240:00	08:00	Ambulatory visit			x				x
	12	264:00	08:00	Ambulatory visit			x				x
	13	288:00	08:00	Ambulatory visit			x				x
	14	312:00	08:00	Ambulatory visit			x				x
	15	336:00	08:00	Ambulatory visit	x		x				x

Visit**	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	$PK_{plasma\ (BI\ 425809)}$	$PK_{plasma\ Donepezil)}$	Safety assessments	12-lead ECG[14]	Vital signs (BP, PR)[14]	Questioning for AEs and concomitant therapy[6]
3 (Treatment D)	1	00:00	08:00	Ambulatory visit[11], admin. 25mg BI 425809	x[2,15]	x[2]	x[2]	x[2,9,10]	x[2]	x[2]	x[2,7]
	2	24:00	08:00	Ambulatory visit[11], admin. 25mg BI 425809							x[2,7]
	3	48:00	08:00	Ambulatory visit[11], admin. 25mg BI 425809							x[2,7]
	4	72:00	08:00	Ambulatory visit[11], admin. 25mg BI 425809		x[8]					x[2,7]
	5	96:00	08:00	Ambulatory visit[11], admin. 25mg BI 425809	x			x[10]	x	x	x[2,7]
	6	120:00	08:00	Ambulatory visit[11], admin. 25mg BI 425809							x[2,7]
	7	144:00	08:00	Ambulatory visit[11], admin. 25mg BI 425809							x[2,7]
	8	168:00	08:00	Ambulatory visit[11], admin. 25mg BI 425809		x[8]					x[2,7]
	9	192:00	08:00	Ambulatory visit[11], admin. 25mg BI 425809	x	x[8]					x[2,7]
		204:00	20:00	Admission to trial site	x[15]						x[7]
	10	214:00	06:00					x[10,2]	x[2]	x[2]	x[2]
		216:00	08:00	**Administration of 10 mg donepezil + 25 mg BI 425809**		x[8]	x[8]				
		217:00	09:00				x				
		218:00	10:00	240 mL fluid intake			x				
		219:00	11:00				x				
		220:00	12:00	240 mL fluid intake, Lunch[3]			x		x	x	x
		222:00	14:00				x				
		224:00	16:00				x				
		226:00	18:00	Dinner[3]			x				
		228:00	20:00				x		x	x	x
	11	234:00	02:00				x				
		240:00	08:00	Administration of 25mg BI 425809	x	x[8]	x[8]	x[10]	x	x	x[2,7]
	12	264:00	08:00	Administration of 25mg BI 425809			x[8]				x[2,7]
	13	288:00	08:00	Administration of 25mg BI 425809			x[8]				x[2,7]
		288:30	08:30	Discharge[11]					x	x	x
	14	312:00	08:00	Ambulatory visit[11], admin. 25mg BI 425809			x[8]				x[2,7]
	15	336:00	08:00	Ambulatory visit[11], admin. 25mg BI 425809	x	x[8]	x[8]	x[10]	x	x	x[2,7]
	16	360:00	08:00	Ambulatory visit[11], admin. 25mg BI 425809			x[8]				x[2,7]
	17	384:00	08:00	Ambulatory visit[11], admin. 25mg BI 425809			x[8]				x[2,7]
	18	408:00	08:00	Ambulatory visit[11], admin. 25mg BI 425809			x[8]				x[2,7]
	19	432:00	08:00	Ambulatory visit[11], admin. 25mg BI 425809			x[8]				x[2,7]
	20	456:00	08:00	Ambulatory visit[11], admin. 25mg BI 425809	x	x[8]	x[8]	x[10]	x	x	x[2,7]
	21	480:00	08:00	Ambulatory visit[11], admin. 25mg BI 425809			x[8]				x[2,7]
	22	504:00	08:00	Ambulatory visit[11], admin. 25mg BI 425809			x[8]				x[2,7]
	23	528:00	08:00	Ambulatory visit[11], admin. 25mg BI 425809			x[8]				x[2,7]
	24	552:00	08:00	Ambulatory visit[11], admin. 25mg BI 425809		x[8]	x[8]	x[10]			x[2,7]
	25	576:00	08:00	Ambulatory visit[11]	x		x		x	x	x
4	36-40	n.a.	n.a.	End of trial examination[4]	x[5]			x[9,10,13]	x	x	x

1. Screening includes subject information, informed consent, physical examination including neurological assessment, check of vital signs, ECG, safety laboratory (including drug screening, alcohol breath test, pregnancy testing in females, and faecal occult blood test), demographics (including determination of body height and weight, smoking status and alcohol history), visual tests, C-SSRS, 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 2 h prior to drug administration.
3. If several actions are indicated at the same time point, the intake of meals will be the last action.
4. End of trial examination includes physical examination, vital signs, ECG, safety laboratory including pregnancy testing in females, recording of AEs and concomitant therapies, faecal occult blood test, C-SSRS and visual tests.
5. Includes immunochemical faecal occult blood (iFOB) test
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.

7. Includes questioning for 'restrictions'
8. Pre-dose PK., i.e. within 10 min prior to the next drug administration
9. C-SSRS
10. Neurological assessment (i.e. Romberg and Unterberger test, assessment of gait, further tests as needed) to be performed at the time points mentioned in the Flow Chart above and at any times CNS adverse events are reported
11. Discharge after confirmation of fitness by the investigator/designee
12. Safety laboratory to be taken within 3 days prior to first trial drug administration of Visit 2 and 3. All results must be available and be checked by the investigator or his/her designee before trial drug administration.
13. Colour discrimination, visual acuity testing, Amsler grid test: tests will be performed at screening, EOT and at any time visual adverse events are reported
14. All blood pressure measurements, as well as pulse rate and ECG will be measured after at least 5 minutes of rest in the supine position
15. Only urine drug screen and alcohol breath test and urine pregnancy testing (female subjects), no safety lab

** There is no wash-out period between Visit 2 and Visit 3. Day 1 of Visit 3 follows directly after day 15 of Visit 2 but these are different days

TABLE OF CONTENTS

ABBREVIATIONS

AD	Alzheimer's Disease
AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
C-SSRS	Columbia Suicide Severity Rating Scale
CA	Competent authority
CI	Confidence interval
CIAS	Cognitive impairment associated with schizophrenia
CL	Total clearance of the analyte in plasma after intravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CNS	Central nervous system
CRF	Case Report Form, paper or electronic (sometimes referred to as 'eCRF')
CRO	Contract Research Organisation
CTM	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DDI	Drug-drug-interaction
DILI	Drug induced liver injury
eECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid

EOT/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	Gastrointestinal
GlyT1	Glycine transporter 1
gMean	Geometric mean
iFOB	Immunochemical Faecal occult blood test
IB	Investigator's brochure
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
MRT	Mean residence time of the analyte in the body after intravenous bolus administration
NMDA	N-methyl-D-aspartate
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference treatment
REP	Residual effect period
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 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

Based on in vitro data, at the highest proposed Phase II dose of 25 mg, BI 425809 and BI 758790 may cause clinically relevant induction of CYP2B6.

1.2.1.2 Non-clinical safety pharmacology and toxicology

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 (7 of them already reported; one trial (1346-0016 [c11975084]) clinically completed, data on file). Two Phase 2 trials (1346-0009 [c03559983] and 1346-0023 [c03632269]) and one Phase 1 trial (1346-0015 [c21363182]) are ongoing.

More than of 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 Investigator's Brochure, 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 Investigator's Brochure, 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

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.

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

1.2.2 Donepezil

Donepezil is a specific and reversible inhibitor of acetylcholinesterase, the predominant cholinesterase in the brain. Current theories on the pathogenesis of the cognitive signs and symptoms of Alzheimer's disease attribute some of them to a deficiency of cholinergic neurotransmission [R15-4794]. Donepezil is indicated for the symptomatic treatment of mild to moderate dementia of the Alzheimer's type and commonly used in this patient population [R18-3913].

In mild to moderate AD the dosing recommendation is a daily dose of 5 mg q.d. which might be increased to a maximum dose of 10 mg q.d.. For tolerability reasons, it is recommended to administer donepezil in the evening and to use an up-titration scheme starting with 5 mg donepezil q.d. and increasing to 10 mg q.d. if needed and well tolerated.

Maximum plasma levels after administration of 10 mg donepezil are reached approximately 3 - 4 hours after oral administration [R15-4794, R18-3913].

The terminal disposition half-life is approximately 70 hours. Following multiple dose administration, steady state is reached within ~3 weeks. Donepezil is mainly excreted (57%) in the urine, both intact (17%) and metabolized, and also via faeces (14.5%). It is extensively metabolized to four major metabolites, of which one, 6-O-Desmethyl-Donepezil has a comparable activity to donepezil, and a number of minor metabolites, of which not all have been identified [R18-3913].

In vitro studies have shown that CYP3A4 and to a minor extent CYP2D6 are involved in the metabolism of donepezil. In a study in healthy volunteers, ketoconazole increased mean donepezil concentrations by about 30 %. In patients with mild – moderate hepatic impairment steady state exposures of donepezil were increased (AUC up to ~ 48%, C_{max} up to ~39%) [R18-3913].
Enzyme inducers such as rifampicin, phenytoin, carbamazepine and alcohol may reduce the levels of donepezil [R15-4794].

In human liver microsomes CYP-450 enzymes 1A2, 2C9, 2C19, 2D6 and 3A4 were inhibited by donepezil with IC_{50} values > 100 µm. In addition, the mean k_i values for CYP-3A4 and CYP-2D6 were calculated to be 131 µm and 47 µm, respectively. Clinical studies have shown that the steady-state C_{max} for the 10 mg dose of donepezil is approximately 164 nm. Since it is anticipated that therapeutic concentrations of donepezil are more than 280-fold lower than the lowest k_i value obtained with CYP-2D6 and almost 800-fold lower than the k_i observed with CYP-3A4, it is expected that donepezil will not inhibit the metabolism of other drugs metabolized by these or any other CYP-450 isoenzymes [R18-3919].

Data from clinical trials in healthy volunteers indicate a good safety profile for daily doses up to 10 mg and an acceptable safety profile for a daily dose of 23 mg. This is in accordance with the sponsor's own experience of a trial in healthy volunteers that received multiple doses of donepezil [c09564954]

- A randomized, double-blind, multiple dose study was investigating the pharmacokinetic and pharmacodynamics profile of donepezil, clinical trials with healthy volunteers. Single daily doses of donepezil (5 and 10 mg) each evening were administered on 28 consecutive days.
  8 subjects received 5 mg donepezil for 28 days, 8 subjects started with 5 mg donepezil and switched thereafter to a daily dose of 10 mg for the remaining 21 days.
  Donepezil was well tolerated by all subjects. The most frequently reported adverse events were headache, gastrointestinal upset, sleep disturbance and lethargy. All were transient, mild and resolved during continued treatment without the need for adjunctive therapy [R05-0853].
- An open-label, randomized, single-dose, two-period crossover study was investigating the bioequivalence of two extended-release tablets of donepezil 23 mg under fasting (n=74) and fed (n= 93) conditions.
  In the fasting study, a total of 154 AEs were reported by 52 subjects. Of all AEs, two (increased neutrophil count and oral herpes) were unexpected and possibly related to the administration of the product. In the fed study, 81 subjects experienced a total of 305 AEs. Of all AEs, four (mydriasis, oral herpes, photophobia, and pupils unequal) were unexpected and possibly related to the administration of the (test or reference) products.
  No subject was withdrawn from the study for safety reasons. There were no deaths or serious adverse events reported. All of the observed AEs were considered to be resolved. Given this information, the study drugs appeared to be well-tolerated and there were no safety concerns observed [R15-4356].
- A study to investigate the pharmacokinetic drug-drug interaction following oral administration of BI 409306 and donepezil in 32 healthy male (n = 17) and female (n = 15) subjects. Part 1 of this trial was performed as a one fixed sequence, open-label trial, in which single doses of BI 409306 and multiple doses of donepezil (5 mg qd for 7 days followed by 10 mg qd for 14 days) were administered, Part 2of this trial was a randomised, open-label, 2-way crossover design, in which single doses of donepezil and multiple doses of BI 409306 were given.
  In Part 1of the trial, i.,e. after multiple doses of donepezil, 16 out of 18 subjects (88.9%) were reported with at least 1 AE that was assessed as drug-related. The most frequently reported drug-related AEs were dizziness and nausea (both 55.6% of subjects), followed by headache and fatigue (both 22.2%). Dizziness was only observed after administration of donepezil alone, whereas nausea and headache were observed after administration of donepezil alone and in combination with BI 409306. As expected visual brightness a known AE of BI 409306 was only observed after BI 409306 administration. Fatigue was observed in all 3 treatment phases.
  All subjects completed the trial except for 1 subject in Part 1 who withdrew during the second treatment period (donepezil administration) because of AEs that were considered not to be drug-related (lower abdominal pain, haematochezia, and ruptured ovarian cyst) [c09564954].

According to [R15-4794, R18-3913], the safety profile mainly results from the cholinergic activity of donepezil, resulting in

- Gastrointestinal symptoms (e.g. nausea, diarrhea, vomiting, abdominal pain, gastric and duodenal ulcers and gastrointestinal hemorrhage)
- Cardiac symptoms (e.g. syncopes, bradycardia, sino-atrial block, atrioventricular block)
- Central-nervous symptoms (e.g. syncopes, dizziness, insomnia, seizures, extrapyramidal symptoms and neuroleptic malignant syndrome)

Further undesirable effects of donepezil include common cold, anorexia, hallucinations, agitations, aggressive behavior, abnormal dreams and nightmares, livery dysfunction including hepatitis, minor increase in serum concentration of muscle creatine kinase, rhabdomyolisis, rash pruritus, muscle cramps, urinary incontinence, headache, fatigue, pain, and accident.

Donepezil

- Is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia
- Should not be co-administered with other cholinergic agonists or antagonists
- Has minor or moderate influence on the ability to drive and use machines
- May have vagotonic effects on the sinoatrial and atrioventricular nodes manifesting as bradycardia or heart block
- As a cholinomimetic may cause bladder outflow obstruction although this was not observed in clinical trials with marketed Aricept (tradename of donepezil in the US)
- As a cholinomimetic may have the potential to cause seizures
- Should be used with care in patients with history of asthma or COPD as cholinomimetics may cause bronchoconstriction

Neuroleptic Malignant Syndrome (NMS):

NMS, a potentially life-threatening condition characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels, has been reported to occur very rarely in association with donepezil, particularly in patients also receiving concomitant antipsychotics. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure.

Cholinergic crisis:

Donepezil overdose can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is possible and may result in death if respiratory muscles are involved.

For a more detailed description of the profile of BI 425809, please refer to the current Investigator's Brochure [c02155957] and for donepezil to the SmPC [R18-3913].

1.2.3 Residual Effect Period

The Residual Effect Period (REP) of BI 425809 is 11 days, the REP for donepezil 15 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

BI 425809 is being developed for the symptomatic treatment of AD. Donepezil is a specific and reversible inhibitor of acetylcholinesterase and is frequently used for the symptomatic treatment of AD.

Both, BI 425809 as well as donepezil are metabolized via CYP3A4. Clinical data show that BI 425809 is a weak inducer of CYP3A4 and at the same time a sensitive CYP3A4 substrate [c02155957]. As donepezil is a commonly used medication in the target population of BI 425809 the potential and relevance of possible drug-drug interaction shall be investigated with this trial to ensure a safe use in upcoming clinical trials as well as in later clinical use in the target population.

1.4 BENEFIT - RISK ASSESSMENT

Participation in this study is without any (therapeutic) benefit for healthy subjects. Their participation in the study, however, is of major importance to the development of BI 425809. The assessment of the drug-drug-interaction (DDI) potential of BI 425809 and donepezil will contribute to a safe clinical use of this GlyT1-inhibitor in patients with Alzheimer`s disease that are also treated with donepezil.

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

Procedure-related risks

The use of an indwelling venous catheter for the purpose of blood sampling may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the wall of the vein. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paresthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to veinipuncture for blood sampling.

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

Drug-related risks and safety measures

Risks related to BI 425809 administration

In Part 2 of this trial, a dose of 25 mg BI 425809 q.d. will be administered over a period of 24 days. Multiple oral doses of 25 mg BI 425809 have already been administered in trial

1346.2 [c02958024] (12 days) and 1346.3 [c03724403] (14 days) and 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 q.d. 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 donepezil administration

Multiple doses of donepezil up to 10 mg were well tolerated in healthy volunteer trials [R15-4355, R05-0853, c09564954]. With single doses up to 23 mg donepezil, the safety profile was still summarized as "well tolerated" and did not raise safety concerns [R15-4356].The safety profile of donepezil is mainly driven by cholinergic effects that in case of overdose may lead to a cholinergic crisis (see Section 1.2.2). Symptoms resulting from the cholinergic effects of donepezil are monitorable and can be adequately treated (see Section 4.2.1).

Risks related to the combined administration of BI 425809 and donepezil

BI 425809 and M530 were determined to be mild in vitro irreversible inhibitors of CYP3A; however, once daily oral administration of BI 425809 (25mg) did not inhibit CYP3A-mediated elimination of midazolam in humans (1346.22 [c08949593]. Mild in vitro reversible inhibition of CYP2D6 (IC_{50} >100 µM) by M530 is not expected to be of clinical impact based on exposures associated with 25 mg qd (C_{max} 25 mg 278 nmol/L, $AUC_{0\text{-}inf}$ 12700nmol*h/L [c02155957] and the minor contribution of CYP2D6 to donepezil metabolism compared to CYP3A4. Therefore an increase of donepezil exposure after BI 425809 administration is not to be expected.

On the opposite, as BI 425809 has been shown clinically to be a weak inducer of CYP3A4 and may therefore reduce levels of donepezil as it has been shown for other enzyme inducers such as rifampicin, phenytoin, carbamazepine and alcohol [R15-4794].

Regarding donepezil, no inhibition of the metabolism of drugs metabolized by CYP-450 isoenzymes is expected at therapeutic doses of donepezil (Section 1.2.2).

In summary, a clinically relevant pharmacokinetic interaction causing elevated exposures of donepezil or BI 425809 is considered unlikely.

Safety measures

- Close monitoring of
  - Adverse events
  - Safety lab (special focus on hepatic parameters, markers of GI bleeding (CRP, haematology, iFOB), CK)
  - ECG (focus on possible vagotonic action of donepezil)
  - Vital signs
- Prohibition to use drugs as concomitant therapy that are known to also trigger gastrointestinal ulcers/hemorrhage, e.g. NSAIDs (Section 4.2.2)
- Availability of rescue medication (atropine) in case of signs and symptoms of cholinergic crisis (see Section 4.2.1).
- Subjects will receive a trial specific emergency card with information for anesthesiologists about the donepezil intake in case of unplanned surgery and potential use of succinylcholine
- As donepezil may impact the ability to operate vehicles and/or machines, subjects participating in Part 1of this trial subjects are not allowed to drive a vehicle or operate machines during Visit 3
- Although only healthy subjects are allowed to enter this trial per se the investigator has to specifically ask subject's for any life-time history of asthma or seizure resulting in exclusion of the subject

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

Overall assessment

Considering the good safety profile of BI 425809 observed so far in healthy subjects, and the safety and tolerability of donepezil up to single doses of 23 mg in healthy volunteers, the unlikelihood of increased drug exposures due to a donepezil-BI 425809 interaction and taking into account the safety measures described in this chapter, the benefit of a successful clinical development of BI 425809 for the treatment of Alzheimer's disease or CIAS is assessed to outweigh the potential risks to healthy subjects participating in this trial that are further considered to be low and acceptable.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of Part 1of this trial is to investigate the effect of co-administration of multiple doses of donepezil on the single-dose pharmacokinetics of BI 425809 in healthy subjects. In Part 2 the main objective is the investigation of the effect of co-administration of multiple doses of BI 425809 on the single-dose pharmacokinetics of donepezil in healthy subjects.

2.1.2 Primary endpoints

Part 1:

The following pharmacokinetic parameters will be determined for BI 425809:

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

Part 2:

The following pharmacokinetic parameters will be determined for donepezil:

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

2.1.3 Secondary endpoint

Part 1:

The following pharmacokinetic parameters will be determined for BI 425809:

- 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)

Part 2:

The following pharmacokinetic parameters will be determined for donepezil:

- 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)

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, including faecal occult blood test
- 12-lead ECG
- Visual tests
- Vital signs (blood pressure, pulse rate)
- Suicidality assessment (C-SSRS, only Part 2)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will consist of two parts and will be performed in healthy male and female subjects. Each subject does only participate in one part of the trial. Both parts are designed as open-label, two-treatment, two-period, one fixed sequence cross-over to investigate the effects of donepezil as perpetrator (Part 1) and as victim (Part 2) in relation to BI 425809.

Part 1 and part 2 are independent from each other as they investigate different pharmacokinetic objectives and endpoints of part 1 would not alter the rationale for part 2. Therefore completion of part 1 is not required to allow start of part 2. This of course does not apply for any safety issues as defined in the stopping criteria (ref Section 3.3.4).

Considering the well-known safety profiles of the selected dose of BI 425809 and donepezil, the unlikelihood of increased drug exposures due to a donepezil-BI 425809 interaction and the already implemented safety measures (ref Section 1.4) treatment of all subjects in one cohort per trial part, i.e. one cohort of 18 subjects in part 1 and one cohort of 14 subjects in part 2, respectively, 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 and be treated not too wide apart in terms of time for better comparability and reducing any possible factors influencing the readout.

In both parts there will be no washout period between treatments.

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

Both parts (Part 1 and Part 2) are 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 analyte 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, donepezil and BI 425809. The fixed-sequence design is not expected to lead to systematic errors in the estimation of the treatment effects, because the trial duration is short enough so that nonspecific time-effects are not expected.

In both part, dosing durations are long enough to achieve steady-state drug exposures of the perpetrator drugs (Part 1: donepezil, Part 2: BI 425809) reliably and to exclude any transient effects. Actually, dosing duration of BI 425809 with 10 days exceeds the time needed to

achieve steady state (after 6 days of dosing) to allow for maximum induction of CYP3A which is delayed compared to achievement of steady state.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 18 (Part 1) and 14 (Part 2) 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 (more than 10 cigarettes or 3 cigars or 3 pipes per day)
14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (consumption of more than 20 g per day for females and 30 g per day for males)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
18. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
19. Inability to comply with the dietary regimen of the trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males or repeatedly greater than 470 ms in females) or any other relevant ECG finding at screening
21. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study

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

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

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

25. History of asthma or obstructive pulmonary disease
26. Clinically relevant cardiac conduction disorders such as sinoatrial or higher degree atrioventricular block and sick sinus syndrome.
27. Bladder outflow obstruction
28. Subjects with increased risk for developing gastrointestinal ulcers (e.g. those with a history of ulcer disease or frequent use of non-steroidal anti-inflammatory drugs)
29. History of macular degeneration or any abnormal finding in visual tests (Amsler grid test, colour discrimination test) at screening
30. Subjects with known hypersensitivity to piperidine derivatives (e.g. astemizol, loratadin, pethidin, loperamid, haloperidol, domperidon)
31. Liver tests (ALT, AST, GGT, AP), Total Bilirubin or Creatinine outside the normal range at the screening examination

Specifically for Part 2:

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

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 5.2.7.2.4.

3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

- The subject wants to discontinue trial treatment, without the need to justify the decision
- 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.
- The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
- The subject can no longer receive trial treatment for medical reasons (such as pregnancy, surgery, adverse events [AEs], or diseases)
- 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
- The subject shows signs and symptoms of cholinergic crisis or neuroleptic malignant syndrome (see Section 1.2.2).
- 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:

- Failure to meet expected enrolment goals overall or at a particular trial site
- 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
- Violation of GCP, or the CTP, or the contract with BI impairing the appropriate conduct of the trial
- 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 per Part discontinue treatment, 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 Ratiopharm GmbH, Germany (donepezil).

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:	Part 1: 0-0-1
	Part 2: 1-0-0
Route of administration:	Oral
Duration of use:	Part 1: single dose on Day 1, Visit 2, and on Day 22, Visit 3
	Part 2: multiple doses on days 1-24, Visit 3

Trial product 2:

Name:	Donepezil-HCl-ratiopharm®
Substance:	Donepezil
Pharmaceutical formulation:	Film-coated tablet
Source:	Ratiopharm GmbH, Germany
Unit strength:	5 mg
Posology:	Part 1: 0-0-1 (Days 1-7, Visit 3) and
	0-0-2 (Days 8-28, Visit 3)
	Part 2: 2-0-0
Route of administration:	Oral
Duration of use:	Part 1: multiple doses on days 1-28, Visit 3
	Part 2: single dose on Day 1, Visit 2 and on Day 10, Visit 3

4.1.2 Selection of doses in the trial

The donepezil dose selected for this trial is the standard clinical dose [R18-3913] 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

Both parts of the trial are designed as open-label, fixed sequence. All subjects participating in one Part 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 fulfill 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 consists of two parts:

Part 1 is an open-label, two-treatment, two-period, one fixed sequence cross-over trial, in which all subjects will first receive BI 425809 (treatment A = Reference 1) alone and then again after multiple doses of donepezil (treatment B = Test 1).

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

Table 4.1.4: 1 Part 1: Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
A (Reference 1)	BI 425809	Tablet	25 mg	1 tablet (Day 1, Visit 2)	25 mg
B (Test 1)	Donepezil	Tablet	5 mg	1 tablet (Day 1-7, Visit 3) q.d. 2 tablets (Day 8-28, Visit 3) q.d.	245 mg
	BI 425809	Tablet	25 mg	1 tablet (Day 22, Visit 3)	25 mg

Part 2 has an open-label two-treatment, two-period, one fixed-sequence cross-over design. In Part 2 all subjects will first receive donepezil (treatment C = Reference 2) alone and then again after multiple doses of BI 425809 (treatment D = Test 2).

The treatments to be evaluated in Part 2 are outlined in Table 4.1.4: 2 below.

Table 4.1.4: 2 Part 2: Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
C **(Reference 2)**	Donepezil	Tablet	5 mg	2 tablets (Day 1, Visit 2)	10 mg
D **(Test 2)**	Donepezil	Tablet	5 mg	2 tablets (Day 10, Visit 3)	10 mg
	BI 425809	Tablet	25 mg	1 tablet (Days 1-24, Visit 3) q.d.	600 mg

Trial medication will be administered to fasted subjects only (for fasting periods please refer to Section 4.2.2.2). 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.

In ***Part 1***, subjects will be kept under close medical surveillance until 38 h following administration of BI 425809 on Day 1, Visit 2 and on Day 22 Visit 3. In addition subjects will remain under medical supervision for about 14 h following the first dose of donepezil on Day 1 Visit 3. This in-house surveillance period can be extended anytime if deemed necessary based on the medical judgement of the investigator.

In ***Part 2***, subjects will be kept under close medical surveillance until at least 72 h following administration of donepezil on Day 1(Visit 2) and Day 10 (Visit 3).

There will be no wash-out period between treatments A/C and B/D in Part 1 and 2, respectively as the extended blood sampling phase already covers a sufficiently long wash-out between the drug administration of treatment A/C and the first drug administration in treatment B/D. Therefore the first day of treatment B/D, i.e. Visit 3, follows immediately after the last day of treatment A/C, i.e. Visit 2, but these two days are not the same day.

For restrictions with regard to diet see Section 4.2.2.2.

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.

PK samples will be labelled in such a way that treatment allocation cannot be derived by the analytical site.

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 donepezil, 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 [R18-3913].

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

No specific rescue medication is foreseen for BI 425809.

In case of a donepezil overdose, general supportive measures should be utilised. Tertiary anticholinergics such as atropine may be used as an antidote for donepezil overdosage. Intravenous atropine sulphate titrated to effect is recommended. An initial dose of 1.0 to 2.0 mg i.v. with subsequent doses based upon clinical response.

No additional treatment is planned. However, in case of adverse events in need of treatment, the investigator can authorise symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all medical evaluation results have returned to an acceptable level.

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:

- 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.

- Drugs that are known to trigger gastrointestinal bleeding/ulcers, e.g. NSAIDs or corticosteroids, are not allowed in Part 2.

- Paracetamol and diclofenac must be avoided as symptomatic therapy of AEs due to its potential liver toxicity.
- The concomitant use of other inhibitors of acetycholinesterase, agonists or antagonists of the cholinergic system is also not allowed. An exception is the use of tertiary anticholinergics such as atropine in case of overdose (see Section 4.2.1).

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 are restricted from consuming any other foods or drinks than those provided by the staff. Standardised meals will be served at the time points described in the Flow Chart.

Part 1:

On all dosing days of Part 1, with the exception of PK profile days, the trial medication will be administered after a fasting period of at least 2 h prior and keeping a post-administration fasting period of at least 1 h. Fluid intake is not allowed from 1 h predose until administration.

On PK profile days (Day 1, Visit 2 and Day 22, Visit 3) subjects will remain fasted for at least 4 hours before administration until 4 hours after and 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.

On PK profile days (Day 1, Visit 2 and Day 22, Visit 3) subjects are requested to go to bed after dinner, lie down (i.e. no declination of the upper body of less than 45 degrees from upright posture except for medical examination or if they need to go to the toilet) and try to sleep. For details regarding post-dose bed resting period see Flow Chart.

Part 2:

In Part 2, administration will be performed following an overnight fast starting no later than 10 h before scheduled dosing. On PK profile days (Day 1, treatment C and Day 10, treatment D), no food is allowed for at least 4 h; from 1 h before drug intake until lunch, fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water served at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until 24 h post-dose, total fluid intake is restricted to 3000 mL. On the remaining days, food is not allowed for at least 1 h after drug administration and fluid intake is not allowed from 1 hour predose until administration.

On PK profile days (Day 1, Visit 2 and Day 10, Visit 3) subjects are not allowed to lie down, i.e. no declination of the upper body of more than 45 degrees from upright posture, except for ECG and blood pressure measurements, during the first 4 h after drug administration.

Part 1 + 2:

On all other in-house days food will be served at standard times if not indicated otherwise in the Flow chart.

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.

Smoking is not allowed during in-house confinement at the trial site.

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.

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 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, informed consent, demographics including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, visual tests, C-SSRS assessment (only for Part 2), 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. Abnormal findings in the neurological and physical examination will be reported as AEs

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) will be measured by a blood pressure monitor (Dinamap, GE Medical Systems, Freiburg, Germany) 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 screening, EOT and any time the subject reports visual adverse events or if it is deemed necessary by the investigator or designee.

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.

Examination of color vision will be carried out at the times 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.

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.

All test results will be documented in the source documents and entered in 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.

5.2.3.2 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.

Visual acuity testing will be carried out at the times 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 in eCRF.

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).

The test results will be documented, and during the course of the study, each post-dose result obtained in a particular subject will be compared to the baseline result.

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).

Any abnormal findings detected in this test during the screening examination will lead to the exclusion of the subject. Any deterioration that occurred during the study will be documented as an AE and an additional ophthalmologic examination should be considered.

All test results will be documented in the source documents and entered in eCRF.

5.2.4 Suicidality monitoring (Part 2 only)

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.

In Part 2 of this trial, with multiple doses of BI 425809, suicidal thoughts and behaviour will be assessed by C-SSRS [R08-1147]. The original Columbia Suicidal Severity Rating scale is shown in Appendix 10.1.

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 in Part 2 and for at least 4 h in Part 1. 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.

Fecal occult blood testing will be performed at the trial site using an immunochemical test kit for hemoglobin (e.g. the PreventID CC test by Preventis GmbH or similar). As subjects may not be able to defecate at the trial site, they may collect the specimen at home and bring the test specimen to the trial site.

Table 5.2.5: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B	C	D
Haematology	Haematocrit	X	X	X	X
	Haemoglobin	X	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X	X
	White Blood Cells/Leucocytes	X	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X	X
Automatic WBC differential, relative and absolute	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal and clinically relevant in the opinion of 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.				
Coagulation	Activated Partial Thromboplastin Time	X	X	X	X
	Prothrombin time – INR (International Normalization Ratio)	X	X	X	X
	Fibrinogen	X	X	X	X
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	X	X	X	X
	ALT [Alanine transaminase] /GPT, SGPT	X	X	X	X
	Alkaline Phosphatase	X	X	X	X
	Gamma-Glutamyl Transferase	X	X	X	X
	Glutamate Dehydrogenase (GLDH)	X	X	X	X
	Creatine Kinase [CK]	X	X	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	X	X	X
	Lactic Dehydrogenase	X	X	X	X
	Lipase	X	--	X	X
	Amylase	X	--	X	X
Hormones	Thyroid Stimulating Hormone	X	--	--	X
	Free T3 - Triiodothyronine	X	--	--	X
	Free T4 – Thyroxine	X	--	--	X
Substrates	Glucose (Plasma)	X	X	X	X
	Creatinine	X	X	X	X
	Bilirubin, Total	X	X	X	X
	Bilirubin, Direct	X	X	X	X
	Protein, Total	X	X	X	X
	Albumin	X	X	X	X
	C-Reactive Protein (Quant)	X	X	X	X
	Uric Acid	X	--	--	X
	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	D
Electrolytes	Sodium	X	X	X	X
	Potassium	X	X	X	X
Urinalysis (Stix)	Urine Nitrite (qual)	X	X	X	X
	Urine Protein (qual)	X	X	X	X
	Urine Glucose (qual)	X	X	X	X
	Urine Ketone (qual)	X	X	X	X
	Urobilinogen (qual)	X	X	X	X
	Urine Bilirubin (qual)	X	X	X	X
	Urine RBC/Erythrocytes (qual)	X	X	X	X
	Urine WBC/Leucocytes (qual)	X	X	X	X
	Urine pH	X	X	X	X
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)				

A: parameters to be determined at Visit 1 of Part 1 and 2 (screening examination)
B: parameters to be determined at Visit 2 and 3 of Part 1 as indicated in the Flow Chart
C: parameters to be determined at Visit 2 and 3 of Part 2 as indicated in the Flow Chart)
D: parameters to be determined at Visit 4 (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 pregnancy tests and drug screening, it is planned to perform these tests during screening only. Pregnancy testing in women will be performed at screening, prior to each treatment period, and as part of the end of trial examination. Drug screening will be performed at screening and prior to each treatment period.

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)
Pregnancy test (urine)	Beta human chorionic gonadotropin (beta-HCG)

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g. Alcotest® 7410, Dräger AG, Lübeck, Germany) will be performed 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 Medizinisches Versorgungszentrum Dr. Klein Dr. Schmitt & Partner, Kaiserslautern, Germany with the exception of the iFOB and the drug screening and pregnancy tests. Thelater ones will be performed at the trial site using Multidrogen Pipettiertest (Diagnostik Nord GmbH, Schwerin) and Alere TestPack+Plus hCG Urine Test, 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 (CardioSoft EKG System, GE Medical Systems, Freiburg, Germany) 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 Muse CV Cardiology System (GE Medical Systems, Freiburg, Germany). Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists).

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

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

5.2.7 Assessment of adverse events

5.2.7.1 Definitions of adverse events

5.2.7.1.1 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.

5.2.7.1.2 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

5.2.7.1.3 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 5.2.7.2, 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.

5.2.7.1.4 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 5.2.7.2.2.

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 eDC system. 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.

5.2.7.1.5 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

5.2.7.1.6 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

5.2.7.2 Adverse event collection and reporting

5.2.7.2.1 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.

5.2.7.2.2 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.

5.2.7.2.3 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.

5.2.7.2.4 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 and consent for the pregnant partner.

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

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

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

For quantification of BI 425809 concentrations in plasma, approximately 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.

For quantification of donepezil plasma concentrations, approximately 2.7 mL of blood will be taken from a forearm vein in a K_2- EDTA-anticoagulant blood drawing tube at the time points listed in the Flow Chart. The EDTA-anticoagulated blood samples will be centrifuged as soon as possible after collection. Centrifugation will last for about 10 minutes (at about 2000 x g to 4000 x g) at 4-8°C. Two plasma aliquots will be prepared and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL plasma whereas the second aliquot should contain the remaining 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 shipment on dry ice to the analytical laboratory, plasma samples will be stored frozen in an upright position at about –20°C or below until transfer to the CRO.

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.

5.3.3 Analytical determinations

5.3.3.1 Analytical determination of analyte plasma concentration

BI 425809 and donepezil 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.

During sample analysis, the bioanalyst will be blinded to subject allocation and will have no access to the randomisation code.

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 as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure.

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 on Day 1 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 and ECG will be be ± 1 h. For laboratory tests the acceptable deviation from the scheduled time will also be ± 30 min, except for the iFOB where it will be ± 12 hours.

If scheduled in the Flow Chart at the same time as a meal, the following recordings have to be done first: 12-lead ECG recordings, vital signs, blood sampling, visual tests, C-SSRS. 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, 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 and physical examination, refer to Sections 5.2.1 to 5.2.7.

6.2.2 Treatment period

Each subject is expected to participate in 2 treatment periods, i.e. Visit 2 and 3. Subjects that take part in Part 1 cannot take part in Part 2 and vice versa.

Part 1

In the morning of Day 1 of Visit 2 and of Day 22 Visit 3, study participants will be admitted to the trial site and kept under close medical surveillance for at least 38 h following drug administration. In addition subjects will be admitted to the trial site prior to the first dose of donepezil (evening of Day 1 Visit 3) and remain under close medical surveillance until the following morning (Day 2, Visit 3). The subjects will then 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.

Part 2

Study participants will be admitted to the trial site in the evening of Day -1 of Visit 2 and of Day 9 Visit 3, and kept under close medical surveillance for at least 72 h following drug administration. After formal assessment and confirmation of their fitness, subjects will then be allowed to leave the trial site. On all other study days, subjects will be treated in an ambulatory fashion.

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

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

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the follow-up period, see Sections 5.2.1 to 5.2.7.
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

Part 1: 25 mg (single dose) of BI 425809 when given alone (Test 1, T1) compared with co-administration with 10 mg (multiple doses) of donepezil (Reference 1, R1), and

Part 2: 10 mg (single dose) of donepezil when given alone (Test 2, T2) compared with co-administration with 25 mg (multiple doses) of BI 425809 (Reference 2, R2),

following oral administration on the basis of the primary and secondary 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.

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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 donepezil (Part 1) and the relative bioavailability of donepezil administered alone compared with co-administration with BI 425809 (Part 2) 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 randomized and 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 or secondary 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 in both Part 1 and Part 2 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 treatmentk,

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 2.1.2) 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.

7.3.2 Secondary endpoint analyses

The secondary endpoints (refer to Section 2.1.3) will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' (001-MCS-36-472) and will be assessed statistically using the same methods as described for the primary endpoints.

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 (any deviations from the randomised treatment will be discussed in the minutes of the Report Planning Meeting).

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

Measurements (such as 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 5.2.7.1), 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 and neurologic findings will be reported as AEs. Fecal occult blood testing results will be listed only.

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 AEs, the completed forms will be stored at the site.

Details for the evaluation of visual tests will be described in the TSAP.

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 32 subjects in the trial (18 in Part 1 and 14 in Part 2), because this sample size is considered sufficient to achieve the aims of this exploratory trial.

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. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to archiving of the CTR.

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

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

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

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

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

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

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

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

- Subject identification: sex, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including dispensing of trial medication

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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

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

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

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

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

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

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

8.6 TRIAL MILESTONES

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

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

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

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at , , 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, responsible for coordinating all required trial activities, in order to

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

The trial medication will be provided by the Clinical Trial Supplies Unit, BI Pharma GmbH & Co. KG, Biberach, Germany. Marketed donepezil will be sourced locally by the CRO.

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

Analyses of BI 425809 concentrations in plasma samples will be performed at , .

Analyses of BI donepizil concentrations in plasma samples will be performed at ,

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 by a CRO appointed by BI according to BI SOPs.

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

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9.1 PUBLISHED REFERENCES

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9.2 UNPUBLISHED REFERENCES

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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 AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		14 March 2019
EudraCT number **EU number**		2018-004806-24
BI Trial number		1346-0029
BI Investigational Medicinal Product(s)		BI 425809
Title of protocol		A study to investigate the effects of donepezil on the pharmacokinetics of BI 425809 and vice versa in healthy male and female subjects (Open-label, two-treatment, two-period, one fixed sequence cross-over design)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		1. Section 3.1 2. Section 3.3.2 3. Section 3.3.3 4. Section 3.3.4.1
Description of change		1. Details on trial conduct added 2. Inclusion criterion 5 was corrected: The requirement to use adequate contraception for at least 30 days prior first drug administration was removed. 3. Exclusion criterion 31 (Normal liver function tests, total bilirubin and creatinine at screening) added 4. Treatment discontinuation in case of elevated liver parameters changed from of "…AST and/or ALT ≥3-fold ULN **AND** an elevation of total bilirubin ≥2-fold ULN…" to "…AST and/or ALT ≥3-fold ULN **OR** an elevation of total bilirubin ≥2-fold ULN…"
Rationale for change		1. Based on the feedback by BfArM, the respective recommendations were included in a revised protocol. This applies for all changes except of the change in section 1.3.2.

		2. The adaption of inclusion criterion 5 was based on EC feedback. EC raised concerns that the 30 days pre-administration period as part of the contraception methods starts before the subjects had consented to trial participation. However, the requirement to use adequate contraception for at least 30 days prior first drug administration is only needed for oral contraceptives as incorrect use may affect the contraceptive effect. Since in this trial oral hormonal contraceptives are not allowed and the other recommended measures, e.g. non-hormonal intra-uterine devices, are immediately effective, a 30 day pre-administration period for the allowed contraceptive methods is not applicable and was deleted. In addition a typo in the Flow Chart of part 2 was deleted.

11.2 GLOBAL AMENDMENT 2

Date of amendment		13 May 2019
EudraCT number **EU number**		2018-004806-24
BI Trial number		1346-0029
BI Investigational Medicinal Product(s)		BI 425809
Title of protocol		A study to investigate the effects of donepezil on the pharmacokinetics of BI 425809 and vice versa in healthy male and female subjects (Open-label, two-treatment, two-period, one fixed sequence cross-over design)

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

Section to be changed		1. Synopsis 2. Flow Chart 3. Section 5.2.5 4. Appendix 10.1
Description of change		1. Trial Clinical Monitor changed to Clinical Trial Leader 2. Alcohol breath test was added to footnote 15 3. Visit 3 was added to footnote B 4. The Screening Version of the C-SSRS was replaced by the Baseline/Screening Version of the C-SSRS
Rationale for change		1. The naming of the function was changed within BI 2. By mistake alcohol breath test as part of the drug screening procedure upon admission was not added. This was corrected 3. An inconsistency between Flow Chart and Footnote B in Section 5.2.5 was corrected 4. By mistake the wrong C-SSRS version for the screening assessment was included. This was corrected

11.3 GLOBAL AMENDMENT 3

Date of amendment		29 May 2019
EudraCT number **EU number**		2018-004806-24
BI Trial number		1346-0029
BI Investigational Medicinal Product(s)		BI 425809
Title of protocol		A study to investigate the effects of donepezil on the pharmacokinetics of BI 425809 and vice versa in healthy male and female subjects (Open-label, two-treatment, two-period, one fixed sequence cross-over design)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		1. Flow Chart 2. Section 5.3.2.1
Description of change		1. A typo in the planned times was corrected 2. The preparation instruction for donepezil samples did not mention that samples should be kept on ice and not longer than for 60 min. This was forgotten by mistake and now added
Rationale for change		A typo in the planned times was corrected and the preparation instruction for donepezil blood samples were clarified.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Medicine		29 May 2019 15:24 CEST
Approval-Therapeutic Area		29 May 2019 15:29 CEST
Author-Trial Clinical Pharmacokineticist		29 May 2019 17:50 CEST
Author-Clinical Trial Leader		03 Jun 2019 08:52 CEST
Author-Trial Statistician		03 Jun 2019 09:13 CEST
Verification-Paper Signature Completion		03 Jun 2019 15:49 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed