Clinical Trial Protocol

	Document Number: c18130121-05
EudraCT No.:	2017-003269-85
BI Trial No.:	1408-0002
BI Investigational Product:	BI 705564
Title:	Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising oral doses of BI 705564 (double-blind, randomised, placebo-controlled, parallel-group design) and evaluation of midazolam interaction (nested, open, fixed-sequence, intra-individual comparison) in healthy male subjects
Lay Title:	This study in healthy men tests how different doses of BI 705564 are taken up in the body and how well they are tolerated. The study also tests how BI 705564 affects the way the body breaks down midazolam.
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Principal Investigator:	Phone: Fax:
Status:	Final Protocol (Revised Protocol (based on global amendment 4))
Version and Date:	Version: 5.0 Date: 08 August 2018

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 705564			
Protocol date: 18 September 2017	**Trial number:** 1408-0002		**Revision date:** 08 August 2018

Title of trial:	Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising oral doses of BI 705564 (double-blind, randomised, placebo-controlled, parallel-group design) and evaluation of midazolam interaction (nested, open, fixed-sequence, intra-individual comparison) in healthy male subjects
Principal Investigator:	
Trial site:	
Clinical phase:	I
Objectives:	(1) To investigate safety, tolerability, pharmacokinetics and pharmacodynamics following multiple rising oral doses of BI 705564 (2) To investigate the effect of BI 705564 on the pharmacokinetics of midazolam given as oral microdose - in dose group **(DG)s 2 to 5**
Methodology:	(1) Double-blind, randomised (within dose group), placebo-controlled, parallel-group comparison (2) Nested, open, fixed-sequence, intra-individual comparison - in **DGs 2 to 5**
No. of subjects:	
total entered:	60* (50 in DGs 1 to 5, and an additional 10 in DG 8)
each treatment:	10 per dose group; 8 on active drug and 2 on placebo
	* Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered may exceed 50, but will not exceed 70 subjects entered.
Diagnosis:	(1) **DGs 1 to 5**: Not applicable (2) **DG 8,**

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Name of finished product: Not applicable			
Name of active ingredient: BI 705564			
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Main criteria for inclusion:	(1) **DGs 1 to 5**: Healthy male subjects, age of 18 to 50 years, body mass index (BMI) of 18.5 to 29.9 kg/m^2 (2) **DG 8, only**		
Test product (1):	BI 705564 film-coated tablet		
Dose:	10 mg (DG 1), 20 mg (DG 2), 40 mg (DG 3), 60 mg (DG 5), 80 mg (DG 4)		
Mode of admin.:	Oral with 240 mL of water after a standard continental breakfast		
Test product (2) (DGs 2 to 5):	Midazolam for injection used as oral solution		
Dose:	75 µg q.d.		
Mode of admin.:	Oral with 240 mL of water after a standard continental breakfast		
Comparator product to test product (1):	Matching placebo		
Dose:	Not applicable		
Mode of admin.:	Oral with 240 mL of water after a standard continental breakfast		
Duration of treatments:	(1) **DGs 1 to 5**: BI 705564 or placebo: Day 1 (1 single dose) and Days 4 to 17 (14 days q.d.) (2) **DGs 2 to 5**: Midazolam: Day -1 and Day 17 (1 single dose, each)		

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Criteria for pharmacokinetics:

<u>Secondary endpoints</u>

(1) BI 705564

After the first dose: $AUC_{\tau,1}$ and C_{max}

After the last dose: $AUC_{\tau,ss}$ and $C_{max,ss}$

(2) Midazolam (**DGs 2 to 5**)

After single doses: AUC_{0-tz} and C_{max}

Criteria for pharmacodynamics:

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Name of finished product: Not applicable			
Name of active ingredient: BI 705564			
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Criteria for safety:	Primary endpoint (1) BI 705564 Safety and tolerability of BI 705564 by the number [N (%)] of subjects with adverse reactions.		

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Name of finished product: Not applicable			
Name of active ingredient: BI 705564			
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Statistical methods:

(1) BI 705564

Descriptive statistics will be calculated for all endpoints.

Dose proportionality of BI 705564 will be explored using a regression model. A 95% confidence interval (CI) for the slope will be computed.

Linearity index will be estimated using a linear model providing a two-sided 95% CI.

Attainment of steady state will be analysed by a repeated measures linear model for trough concentrations (C_{min}) of BI 705564 with dose as an additional covariate, if permissible.

(2) Midazolam (**DGs 2 to 5**)

Descriptive statistics will be calculated for all endpoints.

Relative bioavailability will be estimated by the ratios of the geometric means (test/ reference) for the secondary endpoints. Additionally, their two-sided 90% 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 is not specified. The statistical model will be an ANOVA on the logarithmic scale including effects for ‘subjects’, and ‘treatment’. CIs will be calculated based on the residual error from ANOVA.

FLOW CHART

(DGs 1 to 5)

Visit	Day	Planned time (relative to first BI 705564 administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK $_{blood}$ [9] BI 705564	PK $_{blood}$ MDZ[9]		12-lead ECG	Vital signs (BP, PR)	Questioning for AEs & concomitant therapy[5]
1	-21 to -5			Screening (SCR)[1]	x				x	x	x
2	-4 to -2	-72:00	08:00	Ambulatory visit	x[6]						x
	-1	-25:30	06:30	**Admission to trial site** and **Allocation to treatment[14]: BI 705564 or placebo**	x[2,15]		x[2, 16]		x[2]	x[2]	x[2]
		-24:30	07:30	Standard continental breakfast							
		-24:00	**08:00**	**Midazolam** administration [16]							
		-23:45	08:15				x[16]				
		-23:30	08:30				x[16]				
		-23:00	09:00				x[16]		x[16]	x[16]	
		-22:30	09:30				x[16]				
		-22:00	10:00	240 mL fluid intake			x[16]		x[16]	x[16]	x[16]
		-21:30	10:30				x[16]				
		-21:00	11:00				x[16]				
		-20:00	12:00	240 mL fluid intake, thereafter lunch[3]			x[16]		x[16]	x[16]	x[16]
		-18:00	14:00				x[16]				
		-16:00	16:00	Snack (voluntary)[3]			x[16]			x[16]	x[16]
		-14:00	18:00	Dinner[3]							
	1	-1:00	07:00		x[2]	x[2]			x[2,8]	x[2]	x[2]
		-0:30	07:30	Standard continental breakfast							
		0:00	**08:00**	**BI 705564** or **placebo** administration							
		0:30	08:30			x					
		1:00	09:00			x			x[8]	x	
		1:30	09:30			x					
		2:00	10:00	240 mL fluid intake		x			x[8]	x	x
		3:00	11:00			x					
		4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x			x[8]	x	x
		6:00	14:00			x					
		8:00	16:00	Snack (voluntary)[3]		x			x[8]	x	x
		10:00	18:00	Dinner[3]							
		12:00	20:00			x			x[8]	x	x
	2	24:00	08:00	Breakfast (voluntary), **discharge from trial site**	x	x			x[8]	x	x
		34:00	18:00	Ambulatory visit		x					x
	3	48:00	08:00	Ambulatory visit		x				x	x
	4	70:30	06:30	**Admission to trial site**	x[2,13]	x[2]			x[2,8]	x[2]	x[2]
		72:00	08:00	**BI 705564** or **placebo** administration[11]							
	5	96:00	08:00	**BI 705564** or **placebo** administration[11]		x[2]				x	x
	6	120:00	08:00	**BI 705564** or **placebo** administration[11]		x[2]			x[8]	x	x

Visit	Day	Planned time (relative to first BI 705564 administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK_{blood} [9] BI 705564	PK_{blood} MID[9]		12-lead ECG	Vital signs (BP, PR)	Questioning for AEs & concomitant therapy[5]
2	7	144:00	08:00	**BI 705564** or **placebo** administration[11]						x	x
	8	168:00	08:00	**BI 705564** or **placebo** administration[11]					x[8]	x	x
	9	192:00	08:00	**BI 705564** or **placebo** administration[11]		x[2]			x[8]	x	x
	10	216:00	08:00	**BI 705564** or **placebo** administration[11]	x				x[8]	x[12]	x
	11	240:00	08:00	**BI 705564** or **placebo** administration[11]		x[2]			x[8]	x[12]	x
	12	264:00	08:00	**BI 705564** or **placebo** administration[11]					x[8]	x[12]	x
	13	288:00	08:00	**BI 705564** or **placebo** administration[11]		x[2]			x[8]	x[12]	x
	14	312:00	08:00	**BI 705564** or **placebo** administration[11]					x[8]	x[12]	x
	15	336:00	08:00	**BI 705564** or **placebo** administration[11]		x[2]			x[8]	x[12]	x
	16	360:00	08:00	**BI 705564** or **placebo** administration[11]		x[2]			x[8]	x[12]	x
	17	383:00	07:00		x[2]	x[7,2]	x[2, 16]		x[8,2]	x[12, 2]	x[2]
		383:30	07:30	Standard continental breakfast							
		384:00	08:00	Last **BI 705564** or **placebo** administration & **Midazolam**[16]							
		384:15	08:15				x[16]				
		384:30	08:30			x[7]	x[16]				
		385:00	09:00			x[7]	x[16]		x[8]	x	
		385:30	09:30			x[7]	x[16]				
		386:00	10:00	240 mL fluid intake	x	x[7]	x[16]		x[8]	x	x
		386:30	10:30				x[16]				
		387:00	11:00			x[7]	x[16]				
		388:00	12:00	240 mL fluid intake, thereafter lunch[3]		x[7]	x[16]		x[8]	x	x
		390:00	14:00			x[7]	x[16]				
		392:00	16:00	Snack (voluntary)[3]		x[7]	x[16]		x[8]	x	x
		394:00	18:00	Dinner[3]							
		396:00	20:00			x[7]			x[8]	x	x
	18	408:00	08:00	Breakfast (voluntary), **discharge from trial site**	x	x[7]			x[8]	x[12]	x
		418:00	18:00	Ambulatory visit		x[7]					x
	19	432:00	08:00	Ambulatory visit		x[7]			x[8]	x	x
	20	456:00	08:00	Ambulatory visit		x[7]					x
3	24 to 27			End of trial (EOT) examination[4]	x				x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening and alcohol breath test), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. Time is approximate. The respective procedure is to be performed and completed within 3 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, body weight, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. AEs/ infections/ bleeding events (as of Day 4) 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.

6. Safety laboratory to be taken and to be medically evaluated within 3 days prior to first administration of study drug. This safety laboratory can be omitted, if the screening examination is performed on Days -6 or -5.
7. At these time points, additional blood samples for metabolite identification will be taken (refer to Section 5.5.2.2). A blank sample is to be taken prior to any medication intake (Day -1).
8. The ECG recording has to be performed as triple at this time point. At baseline (Day 1 at -1:00) three pre-dose triplicate ECGs within 10 min are to be recorded.
9. Sampling times and periods may be adapted based on information obtained during the trial (e.g. preliminary PK data) including addition of samples and visits as long as the total blood volume taken does not exceed 500 mL per subject.

11. After a standard continental breakfast
12. Including oral body temperature
13. Including drug screening and alcohol breath test
14. Allocation to treatment may be performed at any time following enrolment but must be completed prior to (first) drug administration.
15. Only drug screening and alcohol breath test.
16. Only DGs 2 to 5

(DG 8/ 28 Days)

Visit	Day	Planned time (relative to first BI 705564 administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK $_{blood}$ [9] BI 705564	Skin Prick Test	CD69 & CD63 $_{blood}$		12-lead ECG	Vital signs (BP, PR)	Questioning for AEs & concomitant therapy[5]
1	-21 to -4			Screening (SCR)[1]	x		x			x	x	x
2	-3 to -1	-72:00	08:00	Ambulatory visit	x[6]		x[6]					x
	1	-1:30	06:30	**Admission to trial site** and **Allocation to treatment[14]: BI 705564 or placebo**	x[2, 15]	x[2]		x[2]		x[2,8]	x[2, 12]	x[2]
		-0:30	07:30	Standard continental breakfast								
		0:00	**08:00**	**BI 705564** or **placebo** administration								
		0:30	08:30			x						
		1:00	09:00			x				x[8]	x	
		1:30	09:30			x						
		2:00	10:00	240 mL fluid intake		x				x[8]	x	x
		3:00	11:00			x						
		4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x				x[8]	x	x
		6:00	14:00			x						
		8:00	16:00	Snack (voluntary)[3]		x				x[8]	x	x
		10:00	18:00	Dinner[3]								
		12:00	20:00			x				x[8]	x	x
	2	23:00	07:00		x	x				x[8]	x	x
		23:30	07:30	Standard continental breakfast								
		24:00	08:00	BI 705564 or placebo administration **discharge from trial site**							x[12]	x
	3	47:00	07:00	Ambulatory visit							x	x
		47:30	07:30	Standard continental breakfast								
		48:00	08:00	**BI 705564 or placebo administration[17]**							x	x
	4	71:00	07:00	Ambulatory visit							x	x
		71:30	07:30	Standard continental breakfast								
		72:00	08:00	**BI 705564** or **placebo** administration[17]							x	x
	5	95:00	07:00	Ambulatory visit							x	x
		95:30	07:30	Standard continental breakfast								
		96:00	08:00	**BI 705564** or **placebo** administration[17]							x	x
	6	119:00	07:00	Ambulatory visit							x	x
		119:30	07:30	Standard continental breakfast								
		120:00	08:00	**BI 705564** or **placebo** administration[17]							x	x
	7	143:00	07:00	Ambulatory visit							x	x
		143:30	07:30	Standard continental breakfast								
		144:00	08:00	**BI 705564** or **placebo** administration[17]							x	x

Visit	Day	Planned time (relative to first BI 705564 administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK $_{blood}$ [9] BI 705564	Skin Prick Test	CD69 & CD63 $_{blood}$		12-lead ECG	Vital signs (BP, PR)	Questioning for AEs & concomitant therapy [5]
2	8	167:00	07:00	Ambulatory visit	x[2]	x[2]	x[2]	x[2]		x[2, 8]	x[12, 2]	x[2]
		167:30	07:30	Standard continental breakfast								
		168:00	08:00	**BI 705564** or **placebo** administration[17]							x	x
	9	191:00	07:00	Ambulatory visit							x	x
		191:30	07:30	Standard continental breakfast								
		192:00	08:00	**BI 705564** or **placebo** administration[17]							x	x
	10	215:00	07:00	Ambulatory visit							x	x
		215:30	07:30	Standard continental breakfast								
		216:00	08:00	**BI 705564** or **placebo** administration[17]							x	x
	11	239:00	07:00	Ambulatory visit							x	x
		239:30	07:30	Standard continental breakfast								
		240:00	08:00	**BI 705564** or **placebo** administration[17]							x	x
	12	263:00	07:00	Ambulatory visit							x	x
		263:30	07:30	Standard continental breakfast								
		264:00	08:00	**BI 705564** or **placebo** administration[17]							x	x
	13	287:00	07:00	Ambulatory visit							x	x
		287:30	07:30	Standard continental breakfast								
		288:00	08:00	**BI 705564** or **placebo** administration[17]							x	x
	14	311:00	07:00	Ambulatory visit							x	x
		311:30	07:30	Standard continental breakfast								
		312:00	08:00	**BI 705564** or **placebo** administration[17]							x	x
	15	335:00	07:00	**Admission to trial site**	x[13, 2]	x[2]				x[8, 2]	x[12, 2]	x[2],
		335:30	07:30	Standard continental breakfast								
		336:00	08:00	**BI 705564** or **placebo** administration								
	16	360:00	08:00	**BI 705564** or **placebo** administration[11]						x[8]	x	x
	17	384:00	08:00	**BI 705564** or **placebo** administration[11]						x[8]	x	x
	18	408:00	08:00	**BI 705564** or **placebo** administration[11]						x[8]	x	x
	19	432:00	08:00	**BI 705564** or **placebo** administration[11]						x[8]	x	x
	20	456:00	08:00	**BI 705564** or **placebo** administration[11]						x[8]	x	x
	21	480:00	08:00	**BI 705564** or **placebo** administration[11]						x[8]	x	x
	22	504:00	08:00	**BI 705564** or **placebo** administration[11]	x[2]	x[2]				x[8, 2]	x[12, 2]	x[2]
	23	528:00	08:00	**BI 705564** or **placebo** administration[11]						x[8]	x	x
	24	552:00	08:00	**BI 705564** or **placebo** administration[11]						x[8]	x	x
	25	576:00	08:00	**BI 705564** or **placebo** administration[11]						x[8]	x	x
	26	600:00	08:00	**BI 705564** or **placebo** administration[11]						x[8]	x	x
	27	624:00	08:00	**BI 705564** or **placebo** administration[11]						x[8]	x	x

Visit	Day	Planned time (relative to first BI 705564 administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK $_{blood}$ [9] BI 705564	Skin prick test	CD 69 & CD 63 $_{blood}$		12-lead ECG	Vital signs (BP, PR)	Questioning for AEs & concomitant therapy [5]
2	28	646:30	06:30		x[2]	x[2]	x[2]	x[2]		x[8,2]	x[12, 2]	x[2]
		647:30	07:30	Standard continental breakfast								
		648:00	08:00	Last **BI 705564** or **placebo** administration								
		648:30	08:30			x						
		649:00	09:00			x				x[8]	x	
		649:30	09:30			x						
		650:00	10:00	240 mL fluid intake	x	x				x[8]	x	x
		651:00	11:00			x						
		652:00	12:00	240 mL fluid intake, thereafter lunch[3]		x				x[8]	x	x
		654:00	14:00			x						
		656:00	16:00	Snack (voluntary)[3]		x				x[8]	x	x
		658:00	18:00	Dinner[3]								
		660:00	20:00			x				x[8]	x	x
	29	671:00	07:00		x	x				x[8]	x[12]	x
		671:30	07:30	Breakfast (voluntary)								
		672:00	08:00	**Discharge from trial site**								
		682:00	18:00	Ambulatory visit		x						x
	30	695:00	07:00	Ambulatory visit		x				x[8]	x	x
	31	719:00	07:00	Ambulatory visit		x						x
3	34 to 37			End of trial (EOT) examination[4]	x					x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening and alcohol breath test), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. Time is approximate. The respective procedure is to be performed and completed within 3 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, body weight, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. AEs/ infections/ bleeding events 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.
6. Safety laboratory and SPT to be taken and to be medically evaluated within 3 days prior to first administration of study drug. These tests can be omitted, if the screening examination is performed on Days -6 to -4.
8. The ECG recording has to be performed as triple at this time point. At baseline (Day 1 at -1:30) three pre-dose triplicate ECGs within 10 min are to be recorded.
9. Sampling times and periods may be adapted based on information obtained during the trial (e.g. preliminary PK data) including addition of samples and visits as long as the total blood volume taken does not exceed 500 mL per subject.

11. After a standard continental breakfast
12. Including oral body temperature
13. Including drug screening and alcohol breath test
14. Allocation to treatment may be performed at any time following enrolment but must be completed prior to (first) drug administration.
15. Only drug screening and alcohol breath test.
17. Administration of study medication on Days 3 to 14 is acceptable within ± 1 h of the planned time.

TABLE OF CONTENTS

ABBREVIATIONS

ACE	Angiotensin converting enzyme
AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve of the analyte in plasma
AUC_{0-24}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 h
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
AUC_{ss}	AUC at steady state
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
β	Slope parameter associated with the power model used to evaluate dose proportionality
BAT	Basophil activation test
BCR	B-cell receptor
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
BTK	Bruton's tyrosine kinase
CA	Competent authority
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady-state

CML	Clinical monitor local
CNS	Central nervous system
CRA	Clinical research associate
CRF	Case report form
CTP	Clinical trial protocol
CTR	Clinical trial report
CTSU	Clinical Trial Supplies Unit
CV	Arithmetic coefficient of variation
CYC	Cyclophosphamide
CYP	Cytochrome P450
DDI	Drug-drug interaction
DG	Dose Group
DILI	Drug induced liver injury
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EOT	End of trial
ESRD	End stage renal disease
FE	Food effect
GCP	Good Clinical Practice
GI	Gastro-intestinal
GLP	Good laboratory practice
gMean	Geometric mean
hERG	Human ether-a-go-go related gene
HPC	Human Pharmacology Centre
HR	Heart rate
IB	Investigator's brochure
IC_{50}	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IPV	Important protocol violation
IRB	Institutional Review Board
ISF	Investigator site file
IV	Intravenous
LC-MS/MS	Liquid chromatography with tandem mass spectrometry

MDZ	Midazolam
MedDRA	Medical Dictionary for Regulatory Activities
MIST	Metabolites in safety testing
MRD	Multiple-rising dose
NOA	Not analysed
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NOR	No valid result
NOS	No sample available
PfOS	Powder for reconstitution of an oral solution
PK	Pharmacokinetic
PKS	Pharmacokinetic set
PO	Per os
PR	Pulse rate
q.d.	*Quaque die*, once daily
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
SLE	Systemic lupus erythematosus
SmPC	Summary of Product Characteristics
SOP	Standard Operation Procedure
SRD	Single-rising dose
ss	(at) steady state
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Test product or treatment

Tab	Tablet
TCPK	Trial clinical pharmacokineticist
TCPKa	Trial clinical pharmacokineticist analyst
TDMAP	Trial Data Management and Analysis Plan
TMF	Trial master file
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
WOCBP	women of child-bearing potential
XLA	X-linked agammaglobulinemia

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Boehringer Ingelheim (BI) is developing BI 705564, an oral, small molecule inhibitor of Bruton's tyrosine kinase (BTK), a member of the Tec family of kinases,

1.2.1.7 Prediction of human pharmacokinetics and therapeutic dose

Information available for DGs 1 to 5

The metabolic clearance (CL) of BI 705564 in human is predicted to be 6.2 mL/min/kg, as determined by scaling of metabolic stability data obtained from incubations with human hepatocytes [n00250613-02]. The V_{ss} in human is predicted to be 2.0 L/kg based on mean body weight-normalized V_{ss} values obtained from PK studies in rat, dog, and monkey. The effective half-life value in human is predicted to be 3.7 h which was estimated based on the projected CL and V_{ss} values. Human bioavailability is predicted to be 10% based on the dog bioavailability data corrected by the difference in estimated hepatic first-pass extraction between dog and human.

the therapeutic dose of BI 705564 (free base) is predicted to be 12 mg q.d. with a corresponding $C_{max,ss}$ of 12 nM and an AUC_{ss} of 89 nM•h.

In study 1408-0001, a single dose of 20 mg under fasting conditions resulted in a mean C_{max} of about 13 nM which is in the range of the predicted therapeutic peak exposure. However, the mean predicted therapeutic systemic exposure of about 90 nM•h was not reached with a single dose of 80mg under fasting conditions (AUC_{0-24} of about72 nM•h). For details, refer to Section 1.2.1.5.

1.2.2 Midazolam (DGs 2 to 5)

Midazolam is a sensitive substrate of CYP3A4, used both in vitro and in vivo as a probe drug for CYP3A4 drug interactions. Absorption is rapid, with maximum concentrations reached around 15 to 30 min. Clearance is also rapid, with an elimination half-life of 1.5 to 2.5 h. The PK of midazolam has been found to be dose proportional over a range of at least 0.001 µg to 3 mg [R17-3022]. For further information, refer to the summary of product characteristics [R17-3087].

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Considerations for DGs 1 to 5

This is the second trial with BI 705564 and the first with multiple dose administrations. The objective of this trial is to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of BI 705564 in male subjects. The chosen population of healthy volunteers using multiple rising oral doses is adequate to provide the basis for the phase 2 clinical development program of BI 705564 This trial will provide pharmacokinetic information in healthy volunteers at steady state exposure.

A currently ongoing phase 1 trial, study 1408-0001 (amended) explored safety and tolerability in healthy male subjects after single doses. At the time of the original CTA submission of this protocol, the dose level of up to 80 mg was completed. Up to this dose level there were no dose-limiting AEs and no SAEs. Since in this single dose study the exposure was going to plateau from 40 mg onwards and the intake of food increased the exposure, the multiple dose study was performed under fed conditions.

Based on in vitro screening data, it cannot be excluded that BI 705564 might be an inactivator and/ or inducer of CYP3A4 (for details, refer to Section 1.2.1.4). To exclude a clinically relevant CYP 3A4 modulation with BI 705564 as perpetrator, an assessment of the effect of BI 705564 on the midazolam metabolism will be conducted in DGs 2 to 5, only. Therefore, these dose groups will receive a microdose of midazolam before start and at the end of treatment with BI 705564.

The safety- and PK data obtained in this study will contribute to define appropriate doses for further clinical studies with BI 705564.

2.2 TRIAL OBJECTIVES

DGs 1 to 5

The primary objective of this trial is to investigate safety and tolerability of BI 705564 in healthy male subjects, following oral administration of multiple rising doses of 10 mg, 20 mg, 40 mg, 60 mg, and 80 mg q.d. over 14 days.

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

In addition, the effect of BI 705564 on the pharmacokinetics of midazolam, given as an oral microdose, will be explored in dose groups 2 to 5.

A description of the endpoints to be determined, and the observations along with specific information as how to collect the data for that information, is provided in Section 5.

Additional considerations for DG 8

2.3 BENEFIT - RISK ASSESSMENT

DGs 1 to 5

Participation in this trial is without any (therapeutic) benefit for healthy subjects. Their participation in the study, however, is of major importance to the development of BI 705564 which is expected to offer advantages compared with other BTK inhibitors in non-oncological indications due to its high selectivity. Subjects in this trial are exposed to risks of study procedures and risks related to the exposure to the trial medication.

2.3.1 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 venipuncture 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.

2.3.2 Drug-related risks and safety measures

Factors of risk may derive from particular knowledge or the lack thereof, regarding (1) the mode of action, (2) the nature of the target, (3) the relevance of animal models and/ or (4) findings in nonclinical safety studies.

2.3.2.1 Mode of action

BTK is a well characterized target with known functions in the immune signaling pathways of B-cells and myeloid cell lineages (refer to Section 1.1). Clinical experience with the marketed BTK inhibitor ibrutinib is available (refer to Sections 1.1). In addition, a 'human model' with loss of function mutations of the BTK gene is known as syndrome XLA.

The immunodeficiency of XLA patients seems to be limited to the decreased levels of circulating antibodies. The resulting (predominant) bacterial infections can be controlled by the application of antibiotics and gammaglobulin substitution, [R17-0404].

Ibrutinib treatment in patients with hematologic malignancies is associated with adverse events including hypertension, thrombocytopenia, and GI complaints (abdominal pain, nausea, diarrhea, and vomiting). As these are not usual features of XLA, they may be related to off-target inhibition by ibrutinib of other enzymes besides BTK. Atrial fibrillation has been reported in patients receiving ibrutinib. The causal relationship of this finding to ibrutinib is not clear. The majority of affected patients had pre-existing cardiovascular disease, and most cases resolved quickly [R17-0124]. Other investigational BTK inhibitors (GDC-0853 and CC-292) were generally well tolerated in phase 1 and phase 2 clinical trials in healthy volunteers and in patients with rheumatoid arthritis. Serious infections, hypertension, thrombocytopenia, and atrial fibrillation were not reported [R17-0165, R17-0166]. All these conditions can be well monitored and are accessible to established therapies.

Haemorrhagic events which also occurred with a thrombocyte count within the reference range were reported under the treatment of ibrutinib. The underlying mechanism is believed to be an inhibition of collagen induced platelet aggregation. Although similar findings are not expect for BI 705564, at this stage of clinical development, subjects will be closely monitored throughout the study for bleeding events which includes also the assessment of platelet function.

BI 705564 binds irreversibly to the BTK binding site (refer to Section 1.2.1). Therefore, the reversibility of physiological (on-target) effects may be more linked to the re-synthesis rate of the BTK protein than to the PK profile of the compound. The time between BTK inhibition and complete recovery of BTK protein in humans is estimated to be between 7 and 10 days, with a recovery of 50% after about 2 to 3 days [R16-0021]. Therefore 7 days seems to be the minimum time between dose groups and from last administration of study drug until the end of trial examination.

2.3.2.2 Nature of the target

The BTK protein is intra-cellularly expressed in myeloid and lymphoid cell lines, predominantly in the immune system (bone marrow, appendix, lymph nodes, tonsils, and spleen), and the lung. [R17-0406] Although on-target effects are unlikely to occur after a multiple doses of BI 705564, they might resemble those seen in XLA patients: Inhibition of B-cell differentiation which may manifest as a transient decrease of peripheral B-cell numbers, transient decrease of immunglobuline levels and, although unlikely, in bacterial infections. Main safety measures performed throughout the study will be: (1) Exclusion of subjects with a repeated decrease of CD19+ B-cell count at screening. (2) Monitoring of white blood cell counts and particularly CD19+ B-cell counts, as well as immunoglobulin levels for at least 7 days after drug administration. (3) Close monitoring for adverse events including symptoms of infections. (4) In case of infections, appropriate clinical evaluation and, if necessary, adequate treatment thereof.

'Down-stream' effects of BTK inhibition are well characterized (refer to Section 1.2.1). How these effects may vary in different populations, e.g. healthy subjects versus diseased patients, young versus elderly, different patient populations, etc., is not known. Also, no information on BTK polymorphisms in healthy individuals and their potential influence on PD effects of BI 705564 or other BTK inhibitors are available.

2.3.2.3 Relevance of animal species and models

Animal models and assays, used during the pharmacological (mice) and toxicological (rats, dogs) assessment of BI 705564 were largely similar to those used for the development and submission of ibrutinib. As such, their relevance for humans was acknowledged by regulatory authorities [R17-0403]. For further information, refer to the current version of the IB [c12104992-03].

2.3.2.4 Findings in nonclinical safety studies

Documents supporting the submission of this trial with BI 705564 were compiled according to Good Clinical Practice (GCP) principles. All pivotal, nonclinical safety studies in support of this clinical trial were conducted in compliance with Good Laboratory Practice (GLP). For further information, refer to the current version of the IB [c12104992-03].

- Safety pharmacology

  A decrease in heart rate was observed at 50 mg/kg/day (NOAEL) in the 4-week dog toxicity study (refer to Section 1.2.1.3) which was not observed at the next lower dose

level of 20 mg/kg/day (NOEL). Reduction of heart rate was also observed after a single dose of 50 mg/kg in the GLP dog telemetry study in dogs but not at a dose of 20 mg/kg. Heart rate will be intensely monitored throughout the study (refer to Flow Chart). For further information, refer to current version of IB [c12104992-03].

- Toxicology

  In the 4-week rat toxicity study (refer to Section 1.2.1.3), a decrease in potassium of 9 to 16 %, as compared to baseline, was observed in all dose groups. Safety laboratory monitoring will include this parameter during the conduct of the study (refer to Flow Chart and Section 5.2.3).

  In the same study, dose independent, only partially reversible effects on the pancreas (i.e. mixed interstitial infiltrates, fibrosis, acinar atrophy, hemorrhage) were noted. These findings could be qualified as rat specific (refer to Section 1.2.1.3) and should not be relevant for humans. Nonetheless, subjects with any medical history of pancreatitis at screening will be excluded from the study. In addition, this organ will be monitored for any inflammatory signs by the determination of amylase and lipase throughout the study. Also, its endocrine function will be monitored by plasma glucose measurements (refer to Flow Chart and Section 5.2.3).

  In the 4-week dog toxicity study (refer to Section 1.2.1.3), a not recovered B-cell depletion (down to 34-43%, as compared to baseline) was noted at the highest dose level of 50 mg/kg/day (NOAEL). Therefore, CD19+ B-cell counts and white blood counts will be monitored throughout the study. At the very dose level of this study, a decrease in heart rate of 11.6 bpm, estimated from the electrocardiograms was observed. Intensive ECG monitoring will be performed after dosing throughout the study (refer to Flow Chart).

2.3.2.5 Drug induced liver injury

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety. Refer also to Section 5.2.2.1 - Adverse events of special interest (AESIs).

2.3.2.6 Risk minimization (safety precautions and stopping rules)

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

DGs 1 to 5

- Careful starting dose selection.
- Escalation factors limited to 2 with increasing doses.
- For safety reasons, each dose group of 10 subjects (8 on active drug, 2 on placebo) will be divided into 2 cohorts of 5 subjects each (4 on active drug, 1 on placebo). Both

cohorts will be dosed in a randomized fashion and each drug administration will be separated by at least 10 min. For orally administered drugs, this is usually a sufficient time frame to observe acute effects.

- For each dose group, the 2 cohorts will be separated by at least 70 h (between the first subjects of each cohort) to account for any intolerability resulting from 3 repeated doses of BI 705564. A continuous safety evaluation, including results of safety laboratories, ECG readings, recordings of vital signs and adverse events will be performed before the individual subject and the subsequent cohort is dosed.
- Interim measurements of BI 705564 plasma levels will be performed. Dose escalation will be stopped, if the gMean of C_{max} or AUC of a dose group exceeds the exposure thresholds of 312 nM for C_{max} or 975 nM•h for AUC, or, if the estimated gMean of above parameters for the next higher dose group is expected to exceed these values. Estimations will be done based on preliminary PK results of preceding dose groups (refer to Section 7.3.5). This should provide a safety margin to the NOAEL of >20 (refer to Table 1.2.1.3: 1).
- If one dose level is safe and shows acceptable tolerability, and if no stopping criterion is met (refer to Section 3.3.4.2), the next higher dose may be given, keeping a minimum dosing interval of 7 days between first subjects of consecutive dose groups due to the irreversible BTK binding of BI 705564 and the time to complete recovery of the BTK protein (refer also to Section 2.3.2.1).
- Should any of the single doses, i.e. 20 mg, 40 mg, 60 mg, and 80 mg, tested in the ongoing study under fed conditions (1408-0001 – amended) be not safe or exceed the predefined above gMean exposure levels, these doses would not be applied in this multiple dose setting.
- Extensive standard safety laboratory measurements including serum electrolytes, serum amylase and lipase, differential white blood counts, as well as CD19+ B-cell and platelet count and bleeding time (modified Ivy method using a Surgicutt) to monitor platelet function will be performed before and after study drug administration (refer to Flow Chart and Section 5.2.3).
- Subjects will be closely monitored for infections and bleeding events throughout the study.
- Repeated triplet 12-lead ECGs are scheduled throughout the study.
- Prior to each dose escalation, a documented safety review will be performed by the Principal Investigator (or an authorized deputy) and the Trial Clinical Monitor (or an authorized deputy). For details, refer to Section 3.1.
- Subjects will be hospitalized throughout the study from Day-1 (treatment with microdose of midazolam in dose groups 2 to 5) to Day 2 (treatment with single dose of BI 705564) and from Day 4 to Day 18 (repeated doses of BI 705564 and a single midazolam microdose on Day 17 in dose groups 2 to 5) and will be discharged only after a formal assessment and confirmation of fitness by an investigator or qualified designee. During in-house confinement, subjects will be under close medical

observation and thoroughly monitored for both, expected and unexpected adverse events.

2.4 OVERALL ASSESSMENT AND CONCLUSION

DGs 1 to 5

BI 705564 is an inhibitor of BTK to be developed for the treatment of LN, SLE and rheumatoid arthritis. Clinical experience has been gained with another BTK inhibitor, ibrutinib, which was approved for the treatment of hematologic malignancies (chronic lymphocytic leukaemia, mantle cell lymphoma, and Waldenström's macroglobulinemia).

Treatment with ibrutinib in patients with hematologic malignancies is associated with adverse events including hypertension, thrombocytopenia, GI complaints and haemorrhagic events which may be related to off-target effects. In contrast, BI 705564 is considered to be a more

selective BTK inhibitor and may have a more favorable safety profile due to less pronounced off-target effects.

Based on numerous published studies [R17-3022, R17-3023], treatment risks with a microdose of midazolam (i.e. 1/100 of a pharmacologically active dose) are considered unlikely.

Considering preclinical and preliminary data obtained in the first in man study of BI 705564 (1408-0001), the well characterized target structure and its physiologic role in B-cell differentiation and function, and taking into account the safety measures described above, participation in this multiple dose regimen does not represent an undue risk to healthy subjects.

Inhibition of BTK in patients with LN, SLE and rheumatoid arthritis is expected to block the stimulation of autoantibody-producing B-cells, and the release of inflammatory cytokines from monocytes and macrophages. By diminishing these harmful, pro-inflammatory pathways, BI 705564 may slow or halt disease progression. Considering the medical need taking into account the potential safety advantage of a highly selective BTK inhibitor, the expected benefit is likely to outweigh the potential risks and justifies exposure of healthy volunteers.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

DGs 1 to 5

A total of 50 healthy male subjects is planned to participate in the trial, according to 5 sequential groups, comprising 10 subjects each. Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered may exceed 50, but will not exceed 70 subjects entered. Such changes may be implemented via non-substantial CTP amendments.

The trial design is depicted in Figure 3.1: 1.

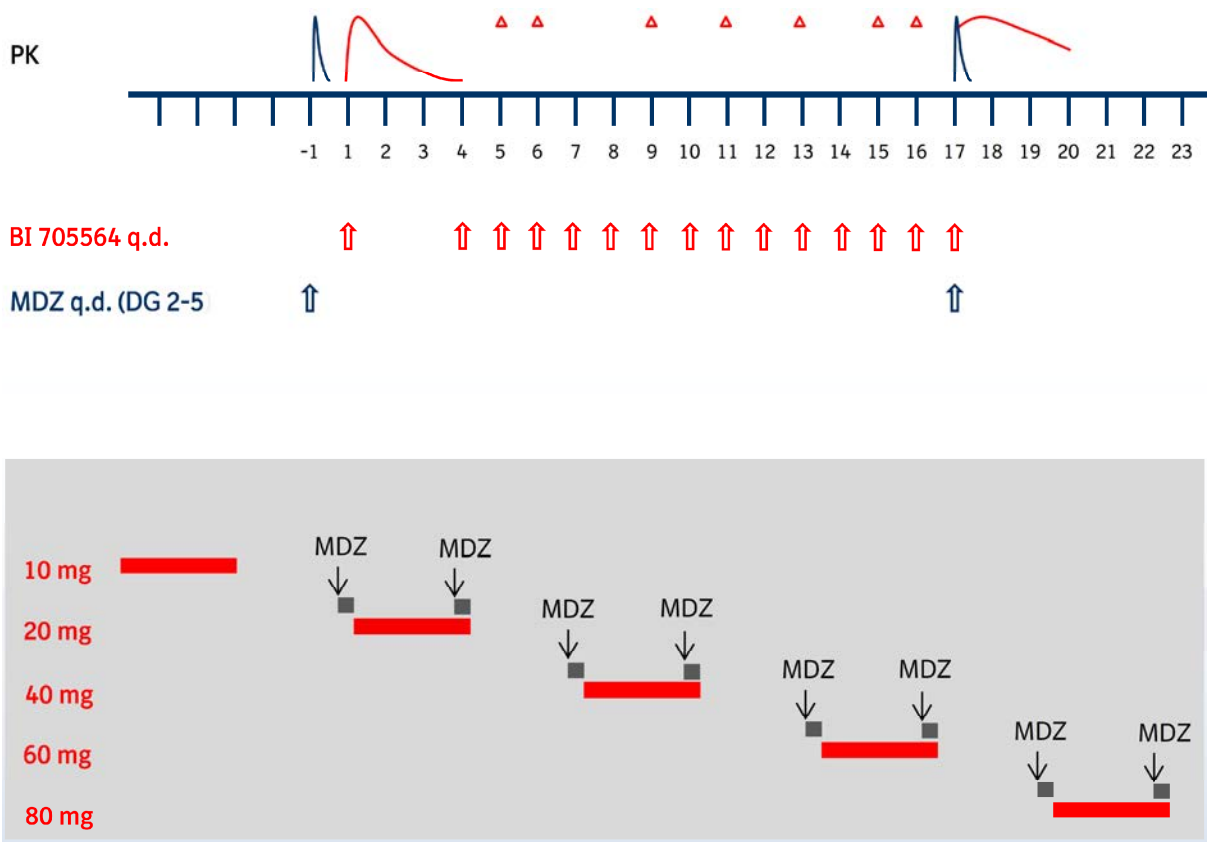


Figure 3.1: 1 Trial design of DGs 1 to 5

BI 705564

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

Table 3.1: 1 Dose groups

Dose Group	**1**	**2**	**3**	**5**	**4**
Daily dose (mg)	10 fed	20 fed	40 fed	60 fed	80 fed
Number of subjects	10	10	10	10	10
Subjects receiving placebo	2	2	2	2	2
Subjects receiving active drug	8	8	8	8	8

* Application of 28 consecutive days

DGs 1 to 5

This segment is designed as a double-blind, randomised (within dose group), placebo-controlled, parallel-group comparison.

Subjects will receive ascending doses of BI 705564 on Day 1 and then over 14 consecutive days from Day 4 to Day 17.

Within each dose group, 8 subjects will receive BI 705564 (active drug) and 2 will receive placebo. Only one dose is tested within each dose group. Each dose group will consist of 2 cohorts (5 subjects each, 4 on active drug and 1 on placebo) which will be treated subsequently for safety reasons. The time interval between these cohorts will be at least 70 h. A continuous safety evaluation, including results of safety laboratories, ECG readings, recordings of vital signs and adverse events will be performed before the individual subject and the subsequent cohort is dosed.

The groups will be investigated consecutively in ascending order of doses, maintaining a time interval of at least 7 days between the last drug administration in the previous dose group and the first drug administration of the subsequent dose group.

The decision to proceed to the next dose group will be based upon the safety, tolerability and PK data of the preceding groups. The next dose will only be given, if, in the opinion of the investigator, no safety concerns arose in the preceding group (i.e. no dose-limiting events occurred) and, if none of the pre-specified trial-specific stopping criteria were met. For more details, refer to Section 3.3.4.2.

A documented safety review must take place prior to each dose escalation. Furthermore, an unscheduled safety review meeting can be requested anytime for any reasonable cause by the Principal Investigator (or an authorised deputy) or the sponsor of the study, e.g. because of any unforeseen adverse events, etc. Dose escalation will only be permitted, if no safety concerns exist in the opinion of the Principal Investigator (or an authorised deputy) and the trial clinical monitor (or an authorised deputy).

The minimum data set for review consists of the following data:

- AEs (incl. monitoring of bleeding events) in the current and preceding dose groups up to at least 48 h of the last dose applied, i.e Visit 2, Day 19, including clinically relevant findings from ancillary safety testing, as listed below. Note: AEs may be ongoing at the time of safety reviews and AE information may be subject to change prior to database lock.
- Results from 12-lead EGG in the current and preceding dose groups up to at least 48 h after the last dose, i.e. Visit 2, Day 19.
- Vital signs in the current and preceding dose groups up to at least 48 h after the last dose, i.e. Visit 2, Day 19.
- Clinical laboratory tests (including bleeding time to monitor platelet function and CD19+ count) in the current and preceding dose groups up to at least Visit 2, Day 18.
- Preliminary PK data for a selected time period, as per Section 7.3.5.

- Check of criteria for stopping subject treatment, as per Section 3.3.4.1.

The decision to escalate the dose will be made jointly by the Principal Investigator (or an authorised deputy) and the trial clinical monitor (or an authorised deputy) after in-depth analysis of all available safety data, especially SAEs (if occurred), AEs (incl. monitoring of bleeding events) and out-of-range laboratory results (if considered clinically significant). Safety reviews can be conducted face-to-face or by video/ telephone conference. The trial clinical monitor is responsible for organization and minutes of the reviews. Minutes will be signed off by the Principal Investigator (or an authorised deputy) and filed in the ISF and TMF.

The investigator (after consultation with the sponsor) is allowed to alter the scheduled dose levels (e.g. add low and/ or intermediate dose levels) on the basis of experience gained during the study, provided the planned and approved highest dose is not exceeded. In this case, the total number of subjects in this trial might increase. The investigator and/ or the sponsor should stop dose escalation in case the safety evaluation leads to concerns that would not allow higher dosing.

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

Midazolam (**DGs 2 to 5**)

This segment is designed as a nested, open, fixed-sequence, intra-individual comparison.

The potential interaction of BI 705564 with a CYP3A4 substrate will be assessed separately in DGs 2 to 5 and in the subjects receiving placebo. This will be conducted in parallel to the multiple dose assessments, using a microdose of midazolam in DGs 2 to 5 (a sensitive CYP3A4 substrate) administered at 2 different time points (Day -1 and Day 17).

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI) Pharma GmbH & Co. KG, Germany.

BI has appointed a Trial Clinical Monitor, responsible for coordinating all required 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 monitors (CML), Clinical Research Associates (CRAs), and participating trial sites.

The trial medication will be provided by the Clinical Trial Supplies Unit (CTSU), BI Pharma GmbH & Co. KG, Biberach, Germany.

The trial will be conducted at
under the supervision of the Principal Investigator.

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

Bleeding time by modified Ivy method (Surgicutt) to monitor platelet function will be measured at . Closure time, measured by PFA-200 (DG 8, only) to further characterise and monitor platelet function will be performed at Gerinnungszentrum Mannheim, Mannheim, Germany. For detailed description, refer to working manual in the ISF.

B-cell CD19+ count will be performed

The analyses BI 705564 concentrations in plasma and urine (DGs 1 to 5) will be performed
.

The analyses midazolam concentrations in plasma (DGs 2 to 5) will be performed at the Department of Drug Metabolism and Pharmacokinetics, BI Pharma GmbH & Co. KG, Biberach, Germany.

The digitally recorded 12-lead ECGs will be sent to

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

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

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

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

DGs 1 to 5

For multiple-rising dose trials, the design described in Section 3.1 is viewed favourable under the provision not to expose subjects involved to undue risks since the main study objective is to investigate safety and tolerability of BI 705564.

With the rising dose design, double-blind conditions regarding the subject's treatment (active drug or placebo) are maintained within each dose group. However, the current dose level will be known to subjects and investigators. The disadvantage of this trial design is a possible observer bias with regard to the dose-depending effects as well as time effects but it has the virtue of minimizing subject risk by sequentially studying ascending doses. As time-effects are expected to be small relative to the differences between the doses in the broad range investigated, unbiased comparisons between treatments can still be expected.

It is standard in trials involving healthy volunteers to include a placebo group as control for the evaluation of safety, tolerability and PD effects. Each dose group consists of 10 subjects with 8 on active treatment, and 2 on placebo. The placebo control group includes all subjects of all dose groups treated with placebo. 8 subjects per active treatment group are in general considered as sufficient for the exploratory evaluation of pharmacokinetics.

After the first dose (single dose segment), a sufficient wash-out period will be included before the second dose (first dose of the multiple dose segment) is administered. This will allow for appropriate calculation of the PK parameters after a single dose administration and for comparison with PK parameters at steady state.

The evaluation of a potential CYP3A4 interaction with BI 705564 using a microdose of midazolam is considered to be acceptable. A microdose of midazolam is not expected to have any pharmacological effects. Therefore, subjects are not exposed to undue risks. Also, the evaluation of the investigational drug should not be influenced. This assessment will allow for better judgement regarding acceptable co-medications in a Proof of Clinical Concept study and later in the phase 3 development.

3.3 SELECTION OF TRIAL POPULATION

DGs 1 to 5

It is planned that 50 healthy male subjects will enter the study. The actual number of subjects entered may exceed the total of 50, if additional intermediate doses will be tested (refer to Section 3.1).Subjects will be recruited from the volunteers' pool of the trial site.

Only male subjects will be included into the study because hitherto no conclusive data on reproductive toxicology are available. With respect to the embryo-fetal risk derived from the treatment of male subjects with BI 705564, where it is theoretically possible that relevant exposure to BI 705564 may be achieved in women of child-bearing potential (WOCBP) from exposure to seminal fluid, male contraception (condom or sexual abstinence) should be used in order to avoid exposure of an existing embryo/ fetus [R16-0373] (refer to Section 3.3.3, exclusion criterion 23).

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

3.3.1 Main diagnosis for study entry

In DGs 1 to 5, the study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. (a) **DGs 1 to 5**: Healthy male subjects according to the assessment of the investigator, based on a complete medical history, a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests;

2. Age of 18 to 50 years (incl.)
3. BMI of 18.5 to 29.9 kg/m^2 (incl.)
4. Signed and dated written informed consent prior to admission to the study in accordance with GCP and local legislation

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) is deviating from normal and judged 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 judged as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy and/ or surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy and simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizure 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 (DGs 1 to 5, only). Allergy to the trial medication or its excipients (all DGs)
11. Use of drugs within 30 days prior to administration of trial medication, if that might reasonably influence the results of the trial (incl. QT/QTc interval prolongation)
12. Participation in another trial where an investigational drug has been administered within 60 days prior to planned administration of trial medication, or current participation in another trial involving administration of investigational drug.
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 30 g per day)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days prior to the administration of trial medication or intended 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 dietary regimen of the trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males) or any other relevant ECG finding at screening
21. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study

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

23. Male subject with WOCBP partner who is unwilling to use male contraception (condom or sexual abstinence) from the first administration of trial medication until 30 days after last administration of trial medication
24. Subjects who, in the investigator's judgement, are perceived as having an increased risk of bleeding, e.g. history of haemorrhagic disorders, clinical relevant petechial bleeding, occult blood in faeces, haematuria in repeated urine tests, trauma or surgery within the

last month, planned surgery during trial participation, history of arteriovenous malformation or aneurysm, history of gastroduodenal ulcer disease or gastrointestinal haemorrhage, history of intracranial, intraocular, spinal, retroperitoneal, or atraumatic intraarticular bleeding, use of drugs that may interfere with haemostasis during trial conduct (e.g. acetylic salicylic acid or other non-steroidal anti-inflammatory drugs)

25. Repeated platelet counts below 100 cells/nL at screening
26. Bleeding times (to monitor platelet function) above reference range at screening
27. Repeated absolute B-cell (CD19+) counts below 40/µL at screening
28. Serum potassium below normal range at screening
29. A history or current clinical signs of acute pancreatitis

For further restrictions, refer to Section 4.2.2 and Table 4.2.2.1: 1.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

An individual subject is to be removed from the trial/ further treatment, if:

1. The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision.
2. The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication (for DGs 1 to 5)
3. The subject is no longer able to participate for other medical reasons (such as surgery, adverse events (AEs), or diseases).
4. An AE or clinically significant laboratory change or abnormality occurred that the investigator judges to warrant discontinuation of treatment. This may include cases of sustained symptomatic hypotension (BP <90/50 mmHg) or hypertension (BP >180/100 mmHg) or of clinically relevant changes in ECG requiring intervention as well as unexplained liver enzyme elevations at any time during the trial.

5. The subject shows an elevation of AST and/ or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/ or needs to be followed up according to the 'DILI checklist' provided in the ISF.
6. The subject shows repeatedly an absolute B-cell (CD19+) count below 40/µL or a platelet count below 100 cells/nL.
7. The subject shows at Day 15 or Day 21 a prolonged bleeding time of above 1440 s, i.e. 3 x ULN (DG 8, only).

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

A subject can also be removed from the trial, if eligibility criteria are being violated or if the subject fails to comply with the protocol (e.g., by non-adherence to dietary rules, or non-attendance at study assessments).

If a subject is removed, or withdraws from the trial prior to first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR). If a subject is removed or withdraws from the trial after first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/ trial database 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 residual effect period (REP) which is defined as 7 days (refer to Section 5.2.2.2), the discontinued subject should, if possible, be questioned for AEs and concomitant therapies at or after the end of the REP in order to ascertain collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject. These discontinuations will be discussed in the CTR.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for any of the following reasons:

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated, if more than 50% of subjects show drug-related and clinically relevant adverse events of moderate or severe intensity or, if at least one drug-related serious adverse event is reported.
2. The expected enrolment goals overall or at a particular trial site are not met.
3. Violation of GCP or the CTP or the contract with BI by a trial site or investigator, disturbing the appropriate conduct of the trial.
4. The sponsor decides to discontinue the further development of the investigational product.

DGs 1 to 5

5. Dose escalation will be stopped as soon as at least 2 subjects at one dose level on active drug showed relevant individual QT prolongation, i.e. a QTc increase of greater 60 ms from baseline in connection with absolute QT or QTc greater than 500 ms which has been confirmed by a repeat ECG recording.
6. Dose escalation will be stopped, if the gMean of C_{max} or AUC of a dose group exceeds the exposure thresholds of 312 nM for C_{max} or 975 nM•h for AUC, or, if the estimated gMean of above parameters for the next higher dose group is expected to exceed these values. Estimations will be done based on preliminary PK results of preceding dose groups (refer to Section 7.3.5).
7. Dose escalation will be stopped, should any of the single doses in study 1408-0001, i.e. 20 mg, 40 mg, 80 mg and 160 mg, tested in the ongoing study under fed conditions be not safe or exceed the predefined above gMean exposure levels (refer to Section 2.3.2.6).

The investigator/ the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

3.3.5 Replacement of subjects

In case some subjects do not complete the trial, the trial clinical monitor 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 study subject number, and will be assigned to the same treatment as the subject he replaces.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

The investigational product has been manufactured

4.1.1 Identity of BI investigational product and comparator products

The characteristics of test (BI 705564)-, reference (placebo)- and probe (Midazolam) product are given below:

Table 4.1.1: 1 Test product

Substance	**BI 705564**
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	10 mg
Posology:	1-0-0 (DG 1); 2-0-0 (DG 2); 4-0-0 (DG 3); 8-0-0 (DG 4); 6-0-0 (DG 5),
Route of administration:	Per os
Duration of use:	DGs 1 to 5: Day 1 (1 single dose) and Days 4 to 17 (14 days q.d.)

Table 4.1.1: 2 Test product

Substance	**BI 705564**
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	100 mg
Posology:	Not used
Route of administration:	Per os
Duration of use:	

Table 4.1.1: 3 Reference product

Substance	**Placebo matching in size and weight to 10 mg film-coated tablet**
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	n.a.
Posology:	1-0-0 (DG 1); 2-0-0 (DG 2); 4-0-0 (DG 3); 8-0-0 (DG 4), 6-0-0 (DG 5),
Route of administration:	Per os
Duration of use:	DGs 1 to 5: Day 1 (1 single dose) and Days 4 to 17 (14 days q.d.)

Table 4.1.1: 4 Reference product

Substance	**Placebo matching in size and weight to 100 mg film-coated tablet**
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	n.a.
Posology:	Not used
Route of administration:	Per os
Duration of use:	

Table 4.1.1: 5 Probe product (**DGs 2 to 5**)

Substance	**Midazolam (Midazolam-ratiopharm®)**
Pharmaceutical formulation:	Solution for injection
Source:	Ratiopharm GmbH, Germany
Unit strength:	5 mg/ 5 mL diluted to 50 µg/mL•1.5 mL (75 µg)
Posology	q.d.
Route of administration:	Per os
Duration of use:	Day -1 and Day 17 (1 single dose, each)

4.1.2 Method of assigning subjects to treatment groups

Prior to the screening visit, subjects will be contacted in writing and informed about the planned visit dates. The subjects willing to participate will be recruited to dose groups according to their temporal availability. As soon as enough subjects have been allocated to 1 of the 12 cohorts (2 cohorts per dose group), the following subjects will be allocated to one of the other dose cohorts. Therefore, the allocation of subjects to dose cohorts is not influenced by trial personnel, but only by the subjects' temporal availability. As the study includes healthy subjects from a homogenous population, relevant imbalances between the dose groups are not expected.

The list of subject and medication numbers will be provided to the trial site in advance. The allocation of subjects to study subject numbers will be performed prior to the first administration of trial medication. For this purpose, the subjects will be allocated to a study subject number by the method 'first come first served'. Once a subject number has been assigned, it cannot be reassigned to any other subject.

The randomisation procedure is described in Section 7.5.

4.1.3 Selection of doses in the trial

Doses, selected for this trial, are intended to cover the sub-therapeutic as well as the estimated therapeutic and supra-therapeutic range and include a safety margin. For details, refer to Section 1.2 and 2.1.

BI 705564

DGs 1 to 5

The dose range for this trial was selected on the basis of the data obtained in the then ongoing first-in-human single rising dose trial 1408-0001. At that time, dose levels up to 80 mg under fasting conditions were well tolerated.

Although a single dose of 20 mg under fasting conditions resulted in a mean C_{max} of about 13 nM (in the range of the predicted therapeutic peak exposure), the mean predicted therapeutic systemic exposure of about 90 nM•h was not reached with a single dose of 80 mg under fasting conditions (AUC_{0-24} of about72 nM•h). The reason for testing further doses under fed conditions (high-fat, high-calorie breakfast) was the observation in the FE part with 10 mg that peak exposure (C_{max}) increased by about 90% and systemic exposure (AUC_{0-24}) by about 60% under food (for details, refer to Section 1.2.1.5).

Due to a short half-life of BI 705564 (refer to Section 1.2.1.5), no major accumulation is expected.

Midazolam ***(DG 2 to 5)***

The dose of midazolam used for the DDI evaluation was chosen to be 75 µg which is within the definition of a microdose, i.e. a $1/100^{th}$ of the therapeutic dose (in case of midazolam 7.5 mg) or 100 µg whichever is smaller. Since midazolam PK is dose proportional ranging from the microdose to the therapeutic dose, the microdose should still be able to accurately predict CYP3A4 DDI liability, while remaining below a pharmacologically active concentration.

A solution for injection was chosen for administration as an oral solution, as a solution for injection is meant to be diluted and, thus, there is data available regarding the stability and compatibility of a diluted solution. Furthermore, the solution for injection contains midazolam in isotonic saline solution, while the oral solution has added excipients, making it less than ideal for such a dilution. Finally, the IV solution has been successfully diluted and administered orally as a microdose in previous clinical studies without any reports of AEs [R17-3022, R17-3023].

4.1.4 Drug assignment and administration of doses for each subject

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

Table 4.1.4: 1 BI 705564 and placebo treatments, oral administration

Dose group	Substance	Pharmaceutical form	Unit strength	Number of units per administration	Total daily dose
1	BI 705564	film-coated tablet	10 mg	1 tablets (10 mg) q.d. for 15 days	10 mg
2	BI 705564	film-coated tablet	10 mg	2 tablets (10 mg) q.d. for 15 days	20 mg
3	BI 705564	film-coated tablet	10 mg	4 tablets (10 mg) q.d. for 15 days	40 mg
4	BI 705564	film-coated tablet	10 mg	8 tablets (10 mg) q.d. for 15 days	80 mg
5	BI 705564	film-coated tablet	10 mg	6 tablets (10 mg) q.d. for 15 days	60 mg
8	BI 705564	film-coated tablet	10 mg	4 tablets (10 mg) q.d. for 28 days	40 mg
1-5	Placebo*	film-coated tablet	--	Identical to active treatment	--

* Subjects receiving placebo are equally distributed across dose groups

DGs 1 to 5

The trial will be divided into two segments (a single dose and a multiple dose segment). During the single dose segment (Days 1 to 3), subjects will receive one single dose of BI 705564 (or placebo) on Day 1. The multiple dose segment will start on Day 4 and subjects will receive doses once daily for 14 days (Days 4 to 17). The doses applied will range from 10 to 80 mg of BI 705564 (or placebo).

Table 4.1.4: 2 Midazolam, oral administration (DGs 2 to 5)

Dose group	Substance	Pharmaceutical form	Unit strength	Number of units per administration	Total daily dose
2-5	Midazolam	Solution for injection	--	1 (Day -1) and 1(Day 17)	75 µg

The oral solutions for dosing midazolam will be prepared according to the instruction given in Appendix 10.1 by pharmacists or qualified pharmacy staff members or qualified medical study personnel at the trial site under the responsibility of the investigator.

The trial medication will be administered to the subjects, while in a sitting/ standing position, as an oral dose together with about 240 mL of water under supervision of the investigating physician or an authorised designee. The so-called four-eye principle (two-person rule) should be applied for administration of trial medication and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise. To ensure a dosing interval of 24 h, the administration of trial medication should take place at the same time every day.

In each treatment, a standard continental breakfast will be served 30 min before drug administration. The meal must be completely consumed prior to drug administration. The composition of the standard continental breakfast is detailed in Table 4.1.4: 3.

Table 4.1.4: 3 Composition of the standard continental breakfast

Ingredients	kcal
1 bread roll	164
15 g butter	113
1 slice of Gouda cheese (approximately 40g)	146
1 slice of meat (approximately 20g)	33
1 cup of decaffeinated coffee or tea (without sugar)	2
Sum[1]	458

[1] The total caloric content was supplied approximately as following: 88 kcal as protein, 133 kcal as carbohydrate, and 237 kcal as fat.

Subjects will be hospitalized and kept under close medical surveillance throughout the study from Day-1 (microdose of midazolam in DGs 2 to 5) to Day 2 (single dose segment with BI 705564) and from Day 4 to Day 18 (multiple dose segment with BI 705564; single dose of microdose of midazolam in DGs 2 to 5). During the first 2 h after drug administration, they are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture except for medical examination), or to sleep. For restrictions with regard to diet, refer to Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

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

Midazolam (**DGs 2 to 5**)

This segment of the 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.

BI 705564

This segment of the trial is designed double-blind with regard to subjects and investigators (as well as the research staff at the trial site) in order to eliminate observer or performance bias. This means avoiding systematic differences in assessments regarding the subject's treatment (active drug or placebo). According to the rising dose design, the current dose level will be known to subjects and investigators.

At the trial site, access to the randomisation schedule is restricted to unblinded pharmacists and pharmacy staff members. Access to the codes will be controlled and documented by a signed confidentiality statement, which will be stored in the TMF. Persons directly involved in the clinical conduct of the trial will not have access to the treatment allocation prior to database lock.

Regarding the sponsor, the database of this trial will be handled open-label, meaning that the trial functions of the sponsor are unblinded (including clinical monitor, data manager, statistician, bioanalyst, pharmacokineticist, pharmacometrician, drug metabolism scientist as well as dedicated CRO personnel). The objective of the trial is not expected to be affected.

The trial site will only be unblinded after locking of the database.

In addition, the trial bioanalyst/ TCPK/ TCPKa will request the randomisation codes prior to official unblinding to perform the interim/ preliminary PK analysis. He or she will confirm in writing that the codes will be treated confidentially.

Within the central ECG lab, the staff involved with interval measurements and morphological analyses will be blinded with respect to the treatment and also with regard to the recording date and time as well as planned time points of the ECGs. The interval measurements for a given subject will be performed in a random and blinded sequence by a single technician. No more than two different blinded readers will evaluate the ECGs of the study.

If an interim safety analysis of ECG data is required, a part of the staff of the ECG laboratory may be unblinded. This part of the staff is strictly separated from that part of the staff which is involved with interval measurements and assessments of single ECGs (blinded).

4.1.5.2 Procedures for emergency unblinding

BI 705564

For the blinded segment of this trial, the investigator will be supplied with a set of sealed envelopes containing the medication codes for each subject according to the randomisation scheme. The envelopes will be kept unopened at the trial site until the end of data collection. An envelope may only be opened in emergency situations when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or to assure safety of trial participants. If the envelope for a subject is opened, the sponsor must be informed immediately. The reason for opening the code break must be documented on the envelope or appropriate CRF page along with the date and the initials of the person who broke the code. At the close-out visit all envelopes are collected.

Midazolam (**DGs 2 to 5**)

As this part of the trial will be conducted in an open fashion, the treatment information will be known. Therefore, no emergency envelopes will be provided.

4.1.6 Packaging, labelling, and re-supply

Drug supplies will be provided by the Department of Pharmaceutical Development of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

The clinical trial supply consists of containers holding the trial medication which are labelled with trial identification. The required information according to the German Drug Law as well as Annex 13/EU GMP Guideline will be provided on the containers. Smaller boxes/ bottles within the clinical trial supply containers will be labelled with:

- BI trial number,
- Name of product and strengths or identification code,
- Pharmaceutical dosage form, quantity of dosage units,
- Route and mode of administration,
- Term ‘For Clinical Trial Use’ (domestic language),
- Sponsor name and address,
- Storage conditions,
- Use-by date,
- Subject or medication number (or for midazolam a placeholder for subject number),
- Batch number.

Ampules will be labelled with the reduced requirements.

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

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended (labelled) storage conditions. Where 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 immediately contacted.

4.1.8 Drug accountability

The investigator/ pharmacist/ investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the IRB / ethics committee,
- Availability of a signed and dated clinical trial contract between the sponsor and the head of the trial 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 as 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. All unused medication will be disposed locally by the trial site upon written authorisation by the clinical monitor. Receipt, usage and disposal must be documented on the respective forms. Account must be given for any discrepancies.

The investigator/ pharmacist/ investigational drug storage manager 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 products and trial subjects. The investigator/ pharmacist will maintain records that document adequately that subjects were provided the doses specified by the CTP, and that reconcile all investigational products received from the sponsor. At the time of disposal, the investigator/ pharmacist must verify that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

DGs 2 to 5

Midazolam will be administered (in dose groups 2 to 5) as a 75 µg dose on Days -1 and 17 to assess the potential influence of BI 705564 on CYP3A4 modulation. For dilution and administration instructions, refer to Appendix 10.1.

There are no special emergency procedures to be followed.

No additional treatment is planned. However, in case of adverse events in need of treatment, the investigator can authorize 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

DGs 1 to 5

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

Paracetamol and acetylsalicylic acid should be avoided. Ibuprofen should preferably be used for treatment of pain such as headache or toothache.

4.2.2.2 Restrictions on diet and life style

DGs 1 to 5

While admitted to the trial site, 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. No food is allowed for at least 4 h after the first and last drug intake (Days -1, 1 and 17). On the remaining days (Days 4 to 16), food is not allowed for at least 2 h after drug intake.

From 1 h before drug intake until lunch, fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water served on Days -1, 1 and 17 at 2 h and 4 h post-dose (mandatory for all subjects).

During the days of urine collection, total fluid intake should be at least 1 litre and should not exceed 3 litres.

Green tea, 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 is collected.

Alcoholic beverages are not permitted starting 48 h before administration of trial medication until after the last PK sample 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 10 h before administration of first trial medication until the end of the in-house period at the trial site.

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.

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured plasma concentrations and urinary excretion (not applicable for DG 8) 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, refer to Section 3.3.4.1.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

5.1.2 Assessment of efficacy

Not applicable.

5.2 SAFETY

A continuous safety evaluation, including results of safety laboratories, ECG readings, recordings of vital signs and adverse events will be performed before the individual subject and the subsequent cohort is dosed.

5.2.1 Endpoints of safety

Primary endpoint to assess safety and tolerability of BI 705564 is the number [N (%)] of subjects with adverse reactions.

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

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.

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, or
- Is a congenital anomaly/birth defect, or
- 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.

AEs considered 'Always Serious'

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the duration between discontinuation of the drug and must be reported as described in Section 5.2.2.2, 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. These events should always be reported as SAEs as described above.

Adverse events of special interest (AESIs)

The term 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 above.
The following are considered as AESIs:

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

  These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained

encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure 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.

With the exception of DILI, no AESIs have been defined for this trial.

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

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 diminished).

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 study drug treatment continues or remains unchanged.

5.2.2.2 Adverse event collection and reporting

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, 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.

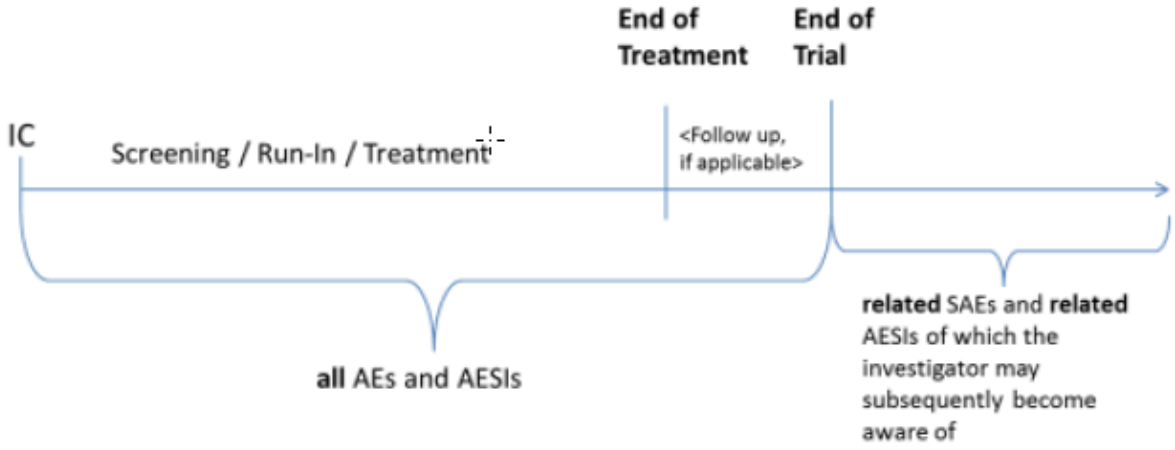
As a minimum, subjects will be questioned for AEs (and concomitant therapies) at the time points indicated in the Flow Chart. Assessment will be made using non-specific questions such as 'How do you feel?'. Specific questions will be asked wherever necessary in order to more precisely describe an AE.

In DGs 1 to 5, as of Day 4, subjects will be questioned and examined for bleeding events at the time points indicated in the Flow Chart.

A careful 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, and intensity of the event as well as 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:
  1. All AEs (serious and non-serious) and all AESIs
  2. The only exception to this rule are AEs (serious and non-serious) and AESIs in phase 1 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:
  1. The investigator does not need to actively monitor the subject for AEs but should only report 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.



The REP for BI 705564, when measurable drug levels or PD effects are still likely to be present after the last administration, is not known at this early stage of development and therefore conservatively defined as 7 days (for details, refer to Section 2.3.2.1). Therefore, all AEs reported until the end of trial examination (last per protocol contact) will be considered on treatment. The follow-up period describes the period of time from the last administration of trial medication until the end of trial examination (last per protocol contact).

AE reporting to 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 h) 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.

Information required

For each AE, the investigator should provide the information requested on the appropriate CRF pages and the BI SAE form (if applicable).
The following should also be recorded as an (S)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 asbaseline conditions and should be collected in the CRF only.

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

5.2.3 Assessment of safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in the Flow Chart after the subjects have fasted for at least 10 h. Overnight fasting is not required at the discretion of the investigator or designee for retests.

The parameters that will be determined are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF, Section 10.

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

The bleeding time will be measured by a modified Ivy method using a Surgicutt (Adult) [R17-3223].

Table 5.2.3: 1 Routine laboratory tests - **DGs 1 to 5**

Functional lab group	**Test name**	**SCR, EOT**	**D-4 to -2**	**D1(pre-), 2 & 4(pre)**	**D10(pre)**	**17(pre-)**	**D17(2h post-)**	**D18**
Haematology	Haematocrit	x	x	x	x	x	x	x
	Haemoglobin	x	x	x	x	x	x	x
	Red blood cell count (RBC)	x	x	x	x	x	x	x
	Reticulocyte count	x						
	White blood cell count (WBC)	x	x	x	x	x	x	x
	Platelet count	x	x	x	x	x	x	x
Automatic WBC differential (relative and absolute)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes	x	x	x	x	x	x	x
Manual differential WBC (if automatic differential WBC is abnormal and clinically relevant in the opinion of the investigator)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes							
Lymphocyte differentiation (relative and absolute)	Lymphocyte panel, including B-cell (CD19+) count	x		x	x	x	x	x
Serum immunoglobulins	IgA, IgG, IgM	x						
Coagulation	Activated partial thromboplastin time (aPTT)	x	x	x	x	x	x	x
	Prothrombin time (Quick's test and INR)	x	x	x	x	x	x	x
	Fibrinogen	x	x	x	x	x	x	x
Platelet function	Bleeding time* with the modified Ivy method using a Surgicutt	x			x		x	
Enzymes	Aspartate transaminase (AST/GOT)	x	x	x	x	x		x
	Alanine transaminase (ALT/GPT)	x	x	x	x	x		x
	Alkaline phosphatase (AP)	x						
	Gamma-glutamyl transferase (GGT)	x	x	x	x	x		x
	Glutamate dehydrogenase (GLDH)	x						
	Creatine kinase (CK), CK-MB, only if CK is elevated	x						
	Lactate dehydrogenase (LDH)	x	x	x	x	x		x
	Lipase	x	x	x	x	x		x
	Amylase	x	x	x	x	x		x
Hormones	Thyroid stimulating hormone (TSH)	x						
Substrates	Plasma glucose	x		x	x	x		x
	Creatinine	x	x	x	x	x		x
	Total bilirubin	x	x	x	x	x		x
	Direct bilirubin	x	x	x	x	x		x
	Total protein	x						
	C-Reactive Protein (CRP)	x	x	x	x	x		x
	Uric acid	x						
	Total cholesterol	x						
	Triglycerides	x						

* Measured up to 30 min

Table 5.2.3: 1 Routine laboratory tests - **DGs 1 to 5** (cont'd)

Functional lab group	**Test name**	**SCR, EOT**	**D-4 to -2**	**D1(pre-), 2 & 4(pre)**	**D10(pre)**	**17(pre-)**	**D17(2h post-)**	**D18**
Electrolytes	Sodium	x	x	x	x	x		x
	Potassium	x	x	x	x	x		x
	Calcium	x						
Urinalysis (Stix)	Urine nitrite	x			x	x	x	x
	Urine protein	x			x	x	x	x
	Urine glucose	x			x	x	x	x
	Urine ketone	x			x	x	x	x
	Urobilinogen	x			x	x	x	x
	Urine bilirubin	x			x	x	x	x
	Urine erythrocytes	x			x	x	x	x
	Urine leukocytes	x			x	x	x	x
	Urine pH	x			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)	x						
Faecal occult blood	Haemoccult Test (Firma Beckman Coulter)	x			x			x

D Day
pre- pre-dose
post- post-dose

The tests listed in Table 5.2.3: 3 and 5.2.3: 4 are exclusionary laboratory tests which may be repeated as required. The results will not be entered in the CRF/ database and will not be reported in the CTR. It is planned to perform these tests during screening only. Drug screening will be performed at screening and prior to each admission to study site.

Table 5.2.3: 3 Exclusionary laboratory tests - **DGs 1 to 5**

Functional lab group	**Test name**	**SCR**	**D-1 & 4(all pre-)**
Drug screening (urine)	Amphetamine/MDA	x	x
	Barbiturates	x	x
	Benzodiazepine	x	x
	Cannabis	x	x
	Cocaine	x	x
	Methadone	x	x
	Methamphetamines/MDMA/XTC	x	x
	Opiates	x	x
	Phencyclidine	x	x
	Tricyclic antidepressants	x	x
Alcohol test (breath)		x	x
Infectious serology (blood)	Hepatitis B surface antigen (qualitative)	x	
	Hepatitis B core antibody (qualitative)	x	
	Hepatitis C antibodies (qualitative)	x	
	HIV-1 and HIV-2 antibody (qualitative), HIV-1 p24-antigen	x	

D Day
pre- pre-dose

To encourage compliance with alcoholic restrictions, a breath alcohol test will be performed at screening and at admission to trial site, and may be repeated at any time during the study at the discretion of an investigator or his/ her designee. The results will not be included in the CTR.

The laboratory tests listed in Table 5.2.3: 1 and 5.2.3: 2 will be performed at with the exception of the urinalysis stix, drug screening and Haemoccult test which will be performed at the trial site using Combur9 Test, AccuSign® DOA 10 Test and Haemoccult Test respectively.

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

5.2.4 Electrocardiogram

5.2.4.1 12-lead resting ECG

Recording

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph at the time points given in the Flow Chart. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven, modified by Mason and Likar (hips and shoulders instead of ankles and wrists). Precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement throughout the study.

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

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

ECGs may be repeated for quality reasons for instance due to alternating current artefacts, muscle movements, or electrode dislocation. For repetition within triplicate ECGs the time window of 180 s applies as well. The repeat ECGs are assigned to the respective scheduled time point. For the repeats due to quality reasons, only the repeated ECG recordings will be sent to the central ECG lab, whereas the initially recorded ECGs will be discarded.

Additional (unscheduled) ECGs may be collected by the investigator for safety reasons. These ECGs are assigned to the prior scheduled time point in the sponsor's database. Unscheduled ECGs will not be included into the statistical analysis of interval lengths.

Data transfer

ECGs, taken at time points specified in the Flow Chart, will be transferred electronically to the central ECG lab for evaluation.

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

Unscheduled ECGs (for safety reasons) will be transferred to the central ECG lab but will not be included into the statistical analysis of interval lengths.

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

Evaluation

1. Central ECG lab

Central ECG lab evaluation (of Visit 2 ECGs only) will be performed for the first of three replicate ECGs per time point given in the Flow Chart. The remaining second and third replicate ECGs will be stored for additional analyses, if required, e.g. by authorities at a later time point.

For baseline, where 3 triplicate ECGs are recorded, only the first triplicate ECG (i.e. 3 single ECGs) will be evaluated.

RR and QT intervals will be determined semi-automatically, whereas PR, QRS intervals and QRS-axis are measured automatically by a validated GE 12-SL-algorithm or equivalent.

Heart rate (HR) and the QT interval corrected for HR (QTc e.g. QTcF and QTcB) will be determined by the sponsor (refer also to TSAP for details).

All semi-automatic interval measurements in one subject will be performed on the same lead. The intervals will be measured from four cardiac cycles (beats) in lead II. If lead II shows a flat T wave or is not measurable for any reason, lead V5 will be used, or if that lead is not measurable, then lead I will be used. The lead actually used will be reported in the CTR.

For automatic interval measurements no lead will be provided.

For blinding arrangements, refer to Section 4.1.5.1. No more than two blinded readers will evaluate all ECGs of the study. ECGs from a particular subject should be evaluated by a single reader. For quality assurance and control of measurements, all ECGs of a subject will be subsequently reviewed by the ECG technician supervisor or his/ her designee to assess the overall variance of the measured intervals and, to detect accidental switching of leads and/ or false subject assignments of the ECGs. After quality control, the fiducial point markings will be reviewed by the cardiologist assigned to the study.

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

2. Trial site

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

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

Abnormal findings, irrespective of whether they originate from central or local evaluation, will be reported as AEs (during the trial) or baseline conditions (at screening), if judged clinically relevant by the investigator. Any ECG abnormalities will be monitored carefully and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor (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.

Oral body temperature will be measured at times, indicated in the Flow Chart, using a standard device.

5.2.5.2 Medical examinations

At screening, the medical examination will include demographics including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR, oral body temperature), 12-lead ECG, laboratory tests, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, body weight and a physical examination.

As part of questioning for AEs, at time points indicated in the Flow Chart, starting with Day 4, subjects will be examined for infections and bleeding events which include, e.g. inspection of skin and visible mucosal surfaces (petechial bleeding or bruising), faecal test for occult blood and haematuria.

5.4 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 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 PK parameters and measurements outlined in Section 5.5 are generally used assessments of drug exposure. The biomarkers and PD parameters and measurements outlined in Section 5.6 are of exploratory nature only.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Date and clock time of drug administration and PK sampling will be recorded in the CRFs.

Actual sampling times will be used for determination of PK parameters.

PK sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g. preliminary PK data) including addition of samples and visits as long as the total blood volume taken per subject does not exceed 500 mL. Such changes would be implemented via non-substantial CTP amendments.

5.5.1 Pharmacokinetic endpoints

The following PK parameters will be determined if feasible:

5.5.1.1 Secondary endpoints

BI 705564

After the first dose:

- $AUC_{\tau,1}$ (area under the concentration-time curve of the analyte in plasma over a uniform dosing interval τ after administration of the first dose)
- C_{max} (maximum measured concentration of the analyte in plasma)

After the last dose:

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

Midazolam (**DGs 2 to 5**)

After the first and last doses:

- C_{max} and $AUC_{0\text{-}tz}$

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

BI 705564

For quantification of BI 705564 plasma concentrations, 2.7 mL of blood will be taken from an antecubital or forearm vein into an K_3-EDTA (tripotassium 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 venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for about 10 min at about 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 plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 120 min, with interim storage of blood samples and aliquots in ice water, on ice or cryoblocks. For each aliquot, the time when the sample was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at about -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 about -20°C or below until analysis.

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

After completion of the trial, the plasma samples may be used for further methodological investigations**,** e.g. for stability testing, assessment of metabolites. However, only data related to the analyte and/ or its metabolite(s) 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 upon the final study report has been signed.

Midazolam (**DGs 2 to 5**)

For quantification of midazolam plasma concentrations, 4 mL of blood will be taken from an antecubital or forearm vein into a K_3-EDTA-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for about 10 min at about 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 1.0 mL plasma the second aliquot should contain the remaining plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 120 min, with interim storage in ice water, on ice or cryoblocks. For each aliquot the time when the sample was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at about -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, plasma samples will be stored at about -20°C or below until analysis.

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

After completion of the trial, the plasma samples may be used for further methodological investigations, e.g., for stability testing, assessment of metabolites. However, only data related to the analyte and/ or its metabolite(s) 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 final study report has been signed.

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of BI 705564 plasma concentration

BI 705564 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.

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As described in Section 4.1.5, the bioanalyst will be unblinded during sample analysis.

5.5.3.3 Analytical determination of Midazolam plasma concentration (**DGs 2 to 5**)

Midazolam concentrations in plasma will be determined by a validated LC-MS/ MS assay. All details of the analytical methods will be available prior to the start of sample analysis.

The analyses will be performed at the Department of Drug Metabolism and Pharmacokinetics, BI Pharma GmbH & Co. KG, Biberach, Germany.

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 end of trial examination are given in the Flow Chart.

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day -1(in DGs 1 to5) and Day 1 (in DG 8) are to be performed and completed within a 3 h-period prior to the trial drug administration (including blank values for PK and biomarkers).

Starting from 72 h post administration, a deviation from the scheduled time for PK and biomarker sampling of ± 30 min is acceptable.

The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 15 min for the first 4 h after trial drug administration and ± 30 min thereafter.

If scheduled at the same time point in the Flow Chart, ECG should be the first and meal the last activity. Furthermore, if several measurements, including venepuncture, are scheduled at the same time, venepuncture should be the last of activities due to its inconvenience to the subject and possible influence on physiological parameters with the exception of screening and EOT visit.

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

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

DGs 1 to5

BI 705564 will be administered on Day 1 and on Day 4 through to Day 17 at 0h (planned time).

Midazolam will be administered on Day -1 and on Day 17 at 0h.

The tolerance for drug administration on Days -1, 1 and 17 will be ± 1 min. On all other treatment days it will be ± 10 min.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

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

6.2.2 Treatment period

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

For details on time points and procedures for sample collection refer to Flow Chart and Section 5.5.2.

Safety measurements performed during the treatment period are specified in Section 5.2 and in the Flow Chart. For details on time points for 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.

DGs 1 to5

Each subject will receive a single dose of BI 705564 or placebo on Day 1 and from Day 4 to Day 17 (14 days).

A single midazolam microdose will be administered on Day -1 and on Day 17 (DGs 2 to 5).

Study participants will be admitted to the trial site the morning of Day -1, at which point the first midazolam microdose will be administered. They will be kept under close medical surveillance for at least 24 h following the first BI 705564 administration on Day 1. Subjects will then be allowed to leave the trial site the morning of Day 2, after formal assessment and confirmation of their fitness by the investigator or designee. On Day 2 in the evening and Day 3 in the morning, the study will be performed in an ambulatory fashion.

In the morning of Day 4, participants will be admitted to the trial site again and kept under close medical surveillance for at least 24 h following the last drug administration on Day 17. After this 14 day hospitalization period, subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or designee. On Days 18 to 20, the study will be performed in an ambulatory fashion.

6.2.3 End of trial period

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the end of trial period, refer to Sections 5.2.2 to 5.2.5.

Subjects who discontinue treatment before the end of the planned treatment period should undergo the end of trial visit.

All abnormal values (including laboratory parameters) that are judged 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 subject's end of trial must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

The end of the trial as a whole is defined by the 'last regular visit completed by last subject' 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.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

BI 705564

DGs 1 to 5

The primary objective of this trial is to investigate the safety and tolerability of BI 705564. This will be achieved by using descriptive statistics for all endpoints, comparing active dose groups to placebo.

The primary endpoint is defined in Section 5.2.1. Inferential statistics are not planned (as explained in Section 7.2).

The secondary objective is the exploration of the pharmacokinetics and pharmacodynamics (PD) of BI 705564. Endpoints, as specified in Sections 5.5.1 (for PK) and 5.7.1 (for PD), will be analysed by descriptive statistics. Secondary endpoints, as defined in Section 5.5.1.1, will be subjected to analysis of dose proportionality by use of the power model.

Trough concentration values will be analysed regarding attainment of steady state as a pre-requisite for calculation of steady state parameters. Additionally, the linearity index will be estimated, if feasible. PD markers and their percentage change from pre-dose will be summarized.

Midazolam (**DGs 2 to 5**)

The relative bioavailability of midazolam in the presence and absence of BI 705564 will be evaluated separately within dose levels 2 to 5 and separately for all subjects receiving placebo. For details, refer to Section 7.3.3.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Safety and tolerability of 6 different DGs (DG 3 will be exposed to 40 mg) of BI 705564 are to be determined on the basis of the investigated parameters in comparison to placebo. It is not planned to test any statistical hypotheses with regard to these variables in a confirmatory sense. Instead, they will be described in their entirety and evaluated by descriptive statistical methods.

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

7.3 PLANNED ANALYSES

All individual data will be listed.

Adherence to the protocol (such as inclusion/ exclusion criteria, times of measurement, compliance with intake of trial medication, treatment dispensing errors, prohibited concomitant medication, completeness and consistency of data) will be checked. Important protocol violations (IPVs) will be identified no later than in the Blinded Report Planning Meeting and provided in the TSAP.

7.3.1 Primary analyses

Analysis of safety and tolerability is described in Section 7.3.4.

7.3.2 Secondary analyses

The secondary parameters (refer to Section 5.5.1) will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472). Analyses will be performed for parent drug.

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

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

The PK parameter analysis set (PKS) includes all subjects in the Treated Set (TS) who provide at least one PK parameter that was not excluded according to the description above.

Assessment of dose proportionality

Dose proportionality will be assessed using the PK endpoints as specified in Section 5.5.1.1.

The basic model for the investigation of dose proportionality will be a power model that describes the functional relationship between the dose and PK endpoints.

$$\exp(Y_{ij}) = \alpha' * \exp(X_i)^{\beta} * \varepsilon'_{ij}$$

The model consists of a regression model applied to log-transformed data. The corresponding ANCOVA model includes the logarithm of the dose as a covariate.

Together with $\alpha' = \exp(\alpha)$ and $\varepsilon'_{ij} = \exp(\varepsilon_{ij})$, taking natural logarithms converts this model to a linear form as follows:

$$Y_{ij} = \alpha + \beta * X_i + \varepsilon_{ij}$$

where

Y_{ij}	logarithm of the PK endpoint for subject j at dose level i; where i = 1, 2, …, 5, j = 1, 2, …, 8,
α	intercept parameter,
β	slope parameter,
X_i	logarithm of dose i,
ε_{ij}	random error associated with subject j at dose level i (assumed to be independent and identically normally distributed).

This equation can be fit as a linear regression model.

Based on the estimate for slope parameter (β), a 2-sided 95% CI for the slope will be computed. Perfect dose proportionality would correspond to a slope of 1. The assumption of a linear relationship between the log-transformed PK endpoint and the log-transformed dose will be checked.

If dose proportionality over the entire dose range investigated cannot be shown, an attempt will be made to identify dose range(s), where dose proportionality can be assumed.

Linearity index

Linearity with respect to multiple administration will be explored using the linearity index (LI) that will be computed as follows:

$$LI = \frac{AUC_{\tau,ss}}{AUC_{0-\infty}}$$

In order to construct a confidence interval for LI, a statistical model using $AUC_{\tau,ss}$ and $AUC_{0-\infty}$ will be set up: A linear model on the logarithmic scale including effects for 'subject' and 'AUC type' can be applied, where 'subject' is a random effect and 'AUC type' a fixed effect.

$$Y_{ij} = \mu + \tau_i + s_j + e_{ij}\ ,\ \text{where}$$

Y_{ij} logarithm of the response (AUC after first dose, AUC after last dose) for subject j and AUC type i; where i = 1 (after first dose) or 2 (after last dose) and j=1, 2,…, 8,

μ the overall mean,

τ_i the AUC type I,

s_j the effect associated with subject j (random effect),

e_{ij} random error associated with subject j at AUC type i (assumed to be independent and identically normally distributed).

A pairwise comparison of both areas via the log transformed difference

$\log(\frac{AUC_{\tau,ss}}{AUC_{0-\infty}}) = \log(AUC_{\tau,ss}) - \log(AUC_{0-\infty})$

will then be performed including calculation of a 2-sided 95% CI. The back transformed point estimate then represents the estimate of LI. Perfect linearity with respect to multiple administrations holds true, if this index equals unity.

Generally, this model will be applied to each dose level separately. If there is evidence that the areas are comparable across dose levels, they can be analysed simultaneously. The corresponding model will then include the log transformed dose as (additional) covariate.

Attainment of steady state

Attainment of steady state will be explored by using the trough concentrations of BI 705564 between Days 4 and 18 and the concentrations taken directly at the end of the first and the last dosing interval for each dose level. Pairwise comparisons of concentrations are performed using 2-sided 95% CIs based on the t-distribution. The calculation is based on a repeated measures linear model on the logarithmic scale.

$$Y_{ij} = \mu + \tau_i + s_j + e_{ij}\ ,\ \text{where}$$

Y_{ij} logarithm of the concentrations for subject j at time i, i = 1, 2, … and j=1, 2,…, 8,

μ the overall mean,

τ_i the effect associated with time point i (repeated effect),

s_j (random) effect of subject j, j=1, 2, ..., 8,

e_{ij} random error associated with subject j at time i (assumed to be independent and identically normally distributed).

Dose can be included as an additional covariate, if there is evidence that the trough concentration profiles are comparable across dose levels.

The model will be used to explore the time to steady state by comparing concentrations pairwise from different time points: log-transformed differences between all subsequent time points ($\log(C_{pre,i}/C_{pre,j}) = \log(C_{pre,i}) - \log(C_{pre,j})$, where $j>i$) will be compared and adjusted means (Least Squares Means) as well as 2-sided 95% CIs will be calculated. Thereafter, these quantities will be back-transformed by exponentiation to give the corresponding (adjusted) ratio and CI.

Comparisons which reveal CIs (for the adjusted ratio) not including 100% will be inspected to determine, if the differences between time points are resulting from not yet attaining steady-state.

For further details, refer to the TSAP (such as selection of covariance structure and comparison of time points).

Graphical displays

To support the analyses of dose proportionality, linearity and attainment of steady state, graphical representations of the data might be created. These might include (but are not limited to) individual time-courses of trough plasma concentrations and the (geometric) mean plasma concentration time profiles.

7.3.4 Safety analyses

Safety will be assessed for the endpoints listed in Section 5.2.1. All treated subjects (i.e., all subjects who received at least one dose of study drug), will be included in the safety analysis. Safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Treatments will be compared in a descriptive way. The placebo control group in the safety evaluation will consist of all placebo treated subjects, regardless of the dose group in which they were treated. As the treatment duration in DG 8 is different from the treatment duration in DGs 1 to 5, all safety outputs for the placebo group will be displayed both, together and separately for DGs 1 to 5 and DG 8. The active treatment groups will be compared to the placebo group in a descriptive way. Tabulations of frequencies/ proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

The analyses will be done by ‘randomised treatment’.

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (refer to 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 'screening', those between first trial medication intake until the end of trial visit will be assigned to the treatment period. These assignments, including the corresponding time intervals, will be defined in detail in the TSAP. Please note that AEs occurring after the last per protocol contact but entered before database lock will be reported to drug safety only and will not be captured in the trial database.

Additionally, further treatment intervals (analysing treatments) may be defined 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 post-study intervals).

AEs 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 (refer to Section 5.2.2.1) and other significant AEs (according to ICH E3) will be listed separately.

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

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

A centralised evaluation of all 12-lead ECGs recordings (refer to Section 5.2.4) will be the basis for the ECG variables QT, HR, QTcF, QTcB, PR, QRS, RR, and further derived ECG parameters. The baseline value of an ECG variable is defined as the mean of the triplicate ECG measurements prior to drug administration. The derivation of the quantitative and qualitative ECG parameters and their analyses will be described in the TSAP.

7.3.5 Preliminary PK analyses

A preliminary analysis of PK parameters (AUC_{0-24} and C_{max} of BI 705564), provided as individual values and geometric means of the first cohort per dose level, will be performed for

- Dose levels 1, 2, 3 and 5 (n) before proceeding to the subsequent dose level 2, 3, 5 and 4

(Note: Data from the first cohorts of the above mentioned dose levels will be sufficient as long as the data from at least 2 subjects on active treatment were available).

In contrast to the final PK/ PD calculations, the preliminary analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows or not. Therefore, minor deviations of preliminary and final results may occur. The preliminary analysis will provide individual and mean concentration/effect-time profiles and summary statistics of individual values without subject identification. The preliminary results will be distributed to the Investigator and the trial team.

Depending on the results of available preliminary PK/ PD analyses, the tolerability and safety of the compound, and changes of dosing schedule (e.g. additional intermediate doses), additional PK/ PD preliminary analysis may be performed based on the request of the Trial Clinical Monitor, the investigator, or Trial Clinical Pharmacokineticist. No formal preliminary PK/ PD report will be written.

No inferential statistical interim analysis is planned. However, after each dose group the investigator (or his/her deputy) is allowed to postpone further dose progression until a preliminary analysis of the data already obtained has been performed.

7.3.6 PK analyses

The PK parameters listed in Section 5.5.1 for drug BI 705564 will be calculated according to the BI SOP ‘Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics’ (001-MCS-36-472).

Subjects who are not included in the PKS (refer to Section 7.3.1) will be reported with their individual plasma/ urine concentrations and individual PK parameters. However, they will not be included in descriptive statistics for plasma/ urine concentrations, PK parameters or other statistical assessment.

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

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

With respect to safety evaluations, it is not planned to impute missing values.

7.4.2 Plasma/urine drug concentration - time profiles (DGs 1 to 5)

Handling of missing PK data will be performed according to the relevant SOP of the Sponsor (001-MCS-36-472).

Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analysed), or BLQ (below the lower limit of quantification) will be displayed as such and not replaced by zero at any time point (this rule also applies to the lag phase, including pre-dose values).

7.4.3 PK parameters

Handling of missing PK data will be performed according to the relevant SOP of the Sponsor (001-MCS-36-472).

For the non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ will be set to zero. All other BLQ values of the profile will be ignored. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.

7.5 RANDOMISATION

Subjects will be randomised within each dose group in a 4:1 ratio which reflects the ratio of subjects receiving active drug to placebo.

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

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

7.6 DETERMINATION OF SAMPLE SIZE

BI 705564

It is planned to include a total of 50 subjects in this trial. The planned sample size is not based on a power calculation. The size of 10 subjects per dose group (8 on active treatment, and

2 on placebo) is commonly used in multiple-rising dose studies of the present type and is in general considered as sufficient for the exploratory evaluation of multiple dose safety and pharmacokinetics.

Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered may exceed 50, but will not exceed 70 subjects entered.

Midazolam (**DGs 2 to 5**)

It is planned to enter a total of 50 subjects in this part of the trial. The planned sample size is not based on a power calculation, but is judged to be adequate to attain reliable results and to fulfil the objectives and requirements of this exploratory trial.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI SOPs.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in a separate agreement between the investigator or the trial site and the sponsor. As a general rule, no trial results should be published prior to finalisation of the CTR.

Insurance Coverage: The terms and conditions of the insurance coverage must be given to each subject and are made available to the investigator via documentation in the ISF.

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND 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 are to be retained by the investigator as part of the trial records. A copy of the signed and dated written informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

The subject must be informed that his personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his medical records may be examined by authorised monitors (Clinical Monitor Local/Clinical Research Associate) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB/ IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/ inspection of this trial may be conducted by the sponsor or sponsor's designees, by IRBs/ IECs, 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.

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the TMF.

8.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. Refer to Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

All data reported in the CRFs must be consistent with the source data or the discrepancies must be explained.

The investigator may need to request previous medical records or transfer records, depending on the trial.

8.3.2 Direct access to source data and documents

The investigator/institution will permit trial-related monitoring, audits, IRB/ IEC review and regulatory inspection, providing direct access to all related source data/documents. CRFs and all source documents, including progress notes (if applicable) and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate/ on site monitor and auditor may review all CRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage period of records

Trial site:

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

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

Individual subject medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Subject confidentiality will be ensured by using subject identification code numbers.

Treatment data may be provided to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated 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, i.e. the CA.

8.6 COMPLETION OF TRIAL

The EC/competent authority in each participating EU member state needs to be notified about the end of the trial (last subject/subject out, unless specified differently in Section 6.2.3 of the CTP) or early termination of the trial.

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n00253487-01 BI 705564: In vitro inhibition studies on cytochrome P450 dependent metabolic reactions. 08 Nov 2016.

n00253544-01 Quantitative whole-body autoradiography in male pigmented rats after single oral administration of [^{14}C]BI 705564. 18 November 2016.

n00255825-01 Assessment of inactivation of the major cytochrome P450 isoforms by BI 705564. 26 Jun 2017.

n00257025-01 Evaluation of induction potential of cytochrome P450 isoforms by BI 705564 in cultured human hepatocytes. 11 Jul 2017.

n00257435-01 Excretion of radioactivity in urine, faeces and bile after oral and intravenous administration of [^{14}C]BI 705564 to rats. 02 Aug 2017.

n00259630-01 [^{14}C]BI 705564: Metabolite profiling and identification in Wistar Han rats. Report in progress.

n00260845-01 [^{14}C]BI 705564: Metabolite profiling and identification in human hepatocytes. Report in progress.

10. APPENDICES

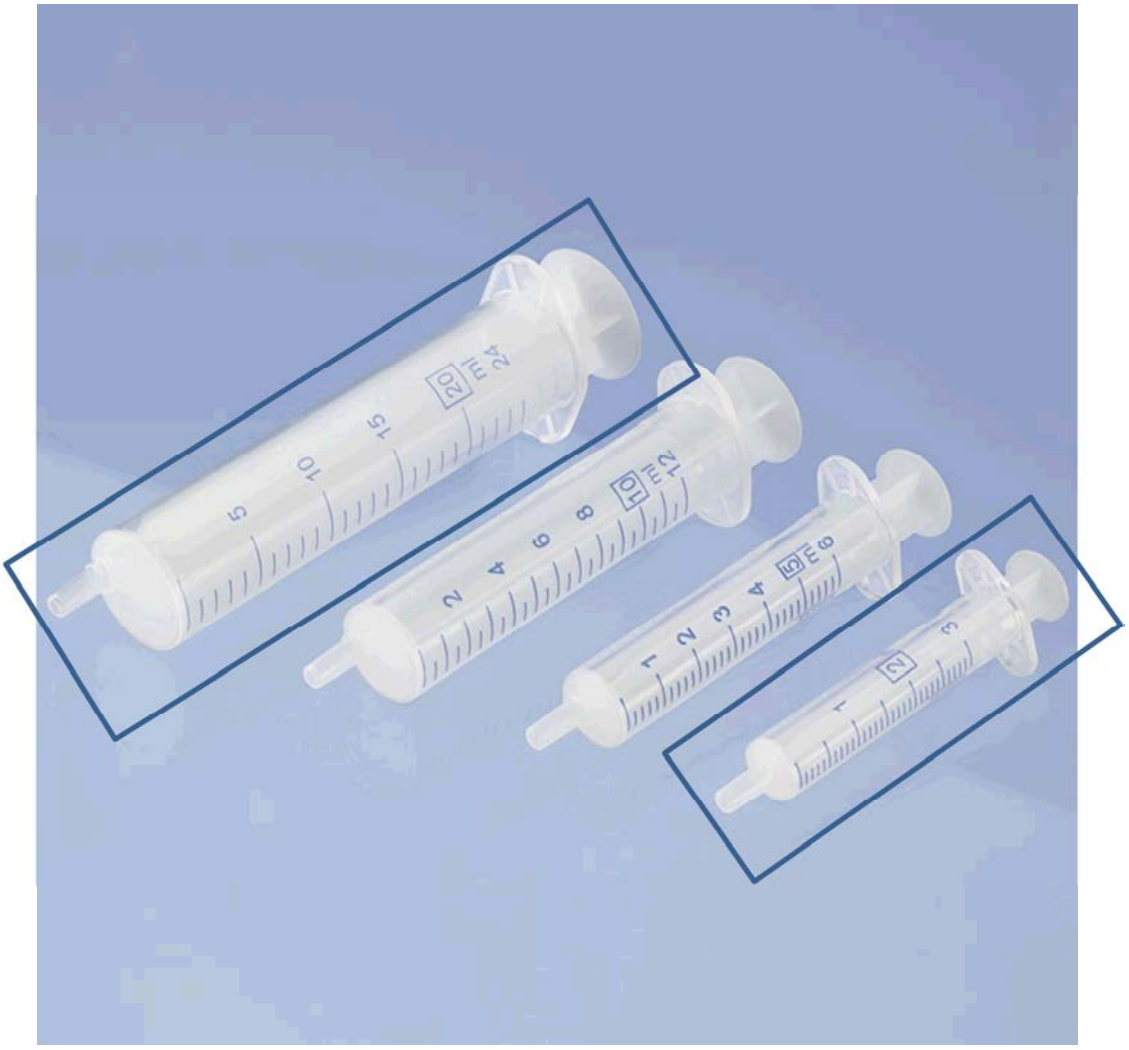
10.1 DILUTION INSTRUCTIONS FOR MIDAZOLAM (DG 2 TO 5)

10.1.1 Required equipment and dosing aids – overview

Dosing and diluting syringes:

1. Henke Sass Wolf 2-part disposable HSW NORM-JECT® Syringes 3 mL
2. Henke Sass Wolf 2-part disposable HSW NORM-JECT® Syringes 24 mL
3. Needle tip

Only CE certified syringes WITHOUT rubber stoppers are to be used!



10.1.2 Dilution procedure

Solution for use with up to 13 subjects

Step 1: Open the commercial isotonic saline solution (0.9% NaCl).

Step 2: Attach a needle tip to the 3 mL syringe and withdraw a bit more than 1 mL of the midazolam solution [concentration: 1 mg/mL] from the originator ampoule using a 3 mL syringe.

Step 3: Remove any air bubbles in syringe (turn upside down and gently push out air by depressing the plunger); ensure that exactly 1 mL midazolam solution remains in the 3 ml syringe.

Step 4: Remove and dispose of needle tip; transfer the full 1 mL of midazolam solution into an appropriate glass container (with cap) by completely depressing the plunger on the 3 mL syringe.

Step 5: Attach a needle tip to the 24 mL syringe and withdraw a bit more than 19 mL isotonic saline solution into the 24 mL syringe; remove air bubbles (see Step 3) and ensure exactly 19 mL isotonic saline solution remains in the 24 ml syringe.

Step 6: Remove and dispose of needle tip; transfer the full 19 mL of isotonic saline solution into the same glass container with the midazolam solution by completely depressing the plunger on the 24 mL syringe.

Step 7: Following addition of the midazolam and saline solutions into the glass container, ensure the glass container is closed using the corresponding cap. The content of the glass container should be mixed thoroughly by swirling gently for approximately 1 min.

Step 8: Extract a little more than 1.5 mL of the dilution solution using a new 3 ml syringe; remove bubbles (see Step 3) and ensure that exactly 1.5 mL of the diluted midazolam solution (final concentration: 50 µg/mL) remains in the 3 mL syringe; the solution is now ready for oral administration.

The final midazolam microdose Oral Solution concentration is 50 ug/mL, for administration of 1.5 mL (75 ug), which can be administered per os directly from the syringe.

10.1.3 In-use stability

The chemical in-use stability of the dilution solution is 24 h after its preparation, incl. storage at room temperature (15-25°C) in Henke Sass Wolf 2-part disposable HSW NORM-JECT® syringes until administration.

10.1.4 Mode of application

Microdoses of Midazolam will be administered orally as specified in the Clinical Trial Protocol (refer to Flow Chart for dosing schedule). 1.5 ml of diluted midazolam solution (concentration 50 µg/mL) will be administered from a syringe, as described above.

Please note that it is the responsibility of the TCM to assure that appropriate supplies are used for administration of a dose and dosing is limited to the allowed dosing range for a specific dose formulation as stated in this Dilution Instruction.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		02 November 2017
EudraCT number		2017-003269-85
BI Trial number		1408-0002
BI Investigational Product(s)		BI 705564
Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising oral doses of BI 705564 (double-blind, randomised, placebo-controlled, parallel-group design) and evaluation of midazolam interaction (nested, open, fixed-sequence, intra-individual comparison) in healthy male subjects
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		Section 2.3.2.6 , Section 3.1 and Section 5.2
Description of change		The following statement was added:' A continuous safety evaluation, including results of safety laboratories, ECG readings, recordings of vital signs and adverse events will be performed before the individual subject and the subsequent cohort is dosed.'
Rationale for change		Specification of methods for continuous safety evaluation before dosing individual subjects and subsequent cohorts due to request of BfArM

Number of global amendment		1
Section to be changed		Throughout the document
Description of change		Minor orthographical and stylistic mistakes were corrected
Rationale for change		N/A

Number of global amendment		2
Date of CTP revision		27 November 2017
EudraCT number		2017-003269-85
BI Trial number		1408-0002
BI Investigational Product(s)		BI 705564
Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising oral doses of BI 705564 (double-blind, randomised, placebo-controlled, parallel-group design) and evaluation of midazolam interaction (nested, open, fixed-sequence, intra-individual comparison) in healthy male subjects
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		Synopsis Flow Chart, footnote 16 Sections 2.1, 2.2, 2.3.2.6 Sections 3.1, Figure 3.1: 1 Sections 4.1.1 (Table 4.1.1: 5), 4.1.4, Table 4.1.4: 2, 4.1.5.1, 4.2.1 Sections 5.5.1.1, 5.5.1.2, 5.5.2.1 Sections 6.1, 6.2.2 Sections 7.1.1, 7.3.3
Description of change		Microdoses of midazolam only be applied in dose groups 2 to 5
Rationale for change		Logistical issues
Section to be changed		Flow Chart
Description of change		Allocation to treatment BI 705564 or placebo will be performed at Day-1, as already described in

Number of global amendment		2
		footnote 14
Rationale for change		Correction of inconsistency
Section to be changed		Throughout the document
Description of change		Minor orthographical and stylistic mistakes were corrected
Rationale for change		N/A

Number of global amendment		3
Date of CTP revision		04 April 2018
EudraCT number		2017-003269-85
BI Trial number		1408-0002
BI Investigational Product(s)		BI 705564
Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising oral doses of BI 705564 (double-blind, randomised, placebo-controlled, parallel-group design) and evaluation of midazolam interaction (nested, open, fixed-sequence, intra-individual comparison) in healthy male subjects
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		☒ An intermediate dose level of 60 mg will be inserted according chapter 3.1 of this CTP. The randomised trial medication of DG 5 (160 mg) will be used for this dose level (only the 10 mg tablets will be administered). Therefore the intermediate dose level will be named DG 5, subject numbers will be 501-510. If DG 5 is safe and well tolerated it may be followed by the original planned DG 4 (80 mg). The originally planned dose level of 160 mg BI 705564 will not be performed.
Section to be changed		Synopsis, 2.2., 2.3.2.6, 3.1, 4.1.1, 4.1.4, and 7.3.5
Description of change		Insertion of intermediate dose level of 60 mg
Rationale for change		In the light of bleeding time prolongation in all subjects on active treatment (expected side effect – see 2.3.2.1) and observed cases of haematuria [1 subject with macrohaematuria (accompanying urinary tract infection), 2 subjects with micro-haematuria (positive sediment in 1 case)] it was decided to reduce the escalation step.

Number of global amendment		4
Date of CTP revision		08 August 2018
EudraCT number		2017-003269-85
BI Trial number		1408-0002
BI Investigational Product(s)		BI 705564
Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising oral doses of BI 705564 (double-blind, randomised, placebo-controlled, parallel-group design) and evaluation of midazolam interaction (nested, open, fixed-sequence, intra-individual comparison) in healthy male subjects
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		New information regarding the additional dose group (DG) 8 is found in most sections of the document.
Description of change		(1) Extension of treatment duration with 40 mg of BI 705564 from 15 to 28 days to further characterize the substance with respect to bleeding time. (2) Additional stopping rule for individual subject: Further application of study medication will be stopped, should the subject show at Day 15 or Day 21 a prolonged bleeding time of above 1440 s (3 x ULN). (3) In addition to bleeding time, the closure time will be measured with the Innovance® PFA-200, using the Dade® PFA Collagen/EPI and the Dade® PFA Collagen/ADP test cartridges to further monitor and characterize platelet function.

Number of global amendment		4
		(6) No application of midazolam as micro-dose, since the influence of midazolam on BI 705564 was already characterized in previous DGs. (7) No measurement of urine PK and plasma metabolites, since these parameters were already sufficiently characterized in previous DGs. (8) Correction of inconsistencies regarding the unblinding of the study. (9) Stylistic adjustments and correction of typographic errors.
Rationale for change		Refer to 'description of change', above

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor		08 Aug 2018 16:36 CEST
Approval-Team Member Medicine		08 Aug 2018 16:57 CEST
Author-Trial Clinical Pharmacokineticist		08 Aug 2018 16:59 CEST
Author-Trial Statistician		09 Aug 2018 09:08 CEST
Approval-Therapeutic Area		10 Aug 2018 04:25 CEST
Verification-Paper Signature Completion		10 Aug 2018 08:43 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed