Clinical Trial Protocol

	Document Number:	**c31764080-02**
EudraCT No.	2020-002506-51	
BI Trial No.	1407-0039	
BI Investigational Medicinal Product	BI 730357	
Title	The effect of multiple doses of BI 730357 on the single dose pharmacokinetics of caffeine, warfarin, omeprazole and midazolam administered orally as a cocktail in healthy subjects (an open-label, two-period fixed sequence design trial)	
Lay Title	A study in healthy people to test whether BI 730357 influences the amount of caffeine, warfarin, omeprazole, and midazolam in the blood	
Clinical Phase	I	
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]	
Principal Investigator	[redacted] Phone: [redacted] Fax: [redacted]	
Status	Final Protocol **(Revised Protocol (based on Global Amendment 1))**	
Version and Date	Version: 2.0	Date: 12. November 2020

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	24 September 2020
Revision date	12 November 2020
BI trial number	1407-0039
Title of trial	The effect of multiple doses of BI 730357 on the single dose pharmacokinetics of caffeine, warfarin, omeprazole and midazolam administered orally as a cocktail in healthy subjects (an open-label, two-period fixed sequence design trial)
Principal Investigator	[redacted]
Trial site	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riß, Germany
Clinical phase	I
Trial rationale	Based on *in vitro* data, BI 730357 and its metabolite CD 6975 are potential inducers of CYP1A2, CYP2C9, CYP2C19 and CYP3A4 at anticipated human therapeutic exposure. [redacted]. Therefore, this trial is aimed to investigate the influence of BI 730357 and its metabolite on the activity of CYP1A2, CYP2C9, CYP2C19, and CYP3A by using *in vivo* probe drugs recommended as sensitive substrates.
Trial objective	To assess the influence of multiple doses of BI 730357 on single dose pharmacokinetics of cytochrome P450 (CYP) probe substrates, as a means of predicting drug-drug interactions. The probe drugs are caffeine (for CYP1A2), warfarin (for CYP2C9), omeprazole (for CYP2C19), and midazolam (for CYP3A).
Trial design	Open-label, non-randomized, two-period fixed sequence design
Trial endpoints	$AUC_{0-\infty}$ and C_{max} as primary endpoints for the probe drugs caffeine, warfarin (specifically S-warfarin), omeprazole and midazolam when administered without BI 730357 and co-administered with BI 730357 at steady-state
Number of subjects	
total entered	16
each treatment	16
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male and female subjects, age of 18 to 55 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)

Trial product 1	Percoffedrinol® N 50 mg Tabletten (tablet strength: 50 mg)
dose	100 mg caffeine (2 tablets) as single doses in treatments T and R
mode of admin.	Oral with 240 mL of water after a standardized meal
Trial product 2	Coumadin® 5 mg (tablet strength: 5 mg)
Dose	10 mg warfarin sodium (2 tablets) as single doses in treatments T and R
mode of admin.	Oral with 240 mL of water after a standardized meal
Trial product 3	Antra MUPS® 20 mg magensaftresistente Tabletten (tablet strength: 20 mg)
Dose	20 mg omeprazole (1 tablet) as single doses in treatments T and R
mode of admin.	Oral with 240 mL of water after a standardized meal
Trial product 4	Midazolam-ratiopharm® 2 mg/mL orale Lösung (strength: 2 mg/mL)
Dose	2 mg midazolam (1 mL) as single doses in treatments T and R
mode of admin.	Oral with 240 mL of water after a standardized meal
Trial product 5	BI 730357 film-coated tablets (tablet strength: 100 mg)
dose	300 mg BI 730357 (3 tablets) twice daily for 20 days in treatment T only
mode of admin.	Oral with 240 mL of water after a standardized meal
Duration of treatment	Treatment R: Drug cocktail alone in Period 1 (Visit 2): Single dose of 100 mg caffeine, 10 mg warfarin, 20 mg omeprazole and 2 mg midazolam administered as drug cocktail (Day 1). Treatment T: Drug cocktail plus BI 730357 in Period 2 (Visit 3): Multiple doses of 300 mg BI 730357 administered twice daily on 20 days (Day -14 to Day 6) combined with a single dose of 100 mg caffeine, 10 mg warfarin, 20 mg omeprazole and 2 mg midazolam administered as drug cocktail on the 15th day of BI 730357 treatment (Day 1, one hour after the morning dose of BI 730357). The cocktail treatments will be separated by a wash-out of at least 20 days.
Statistical methods	For each probe drug, the effect of drug-drug interactions will be estimated by the ratios (co-administration with BI 730357 vs. probe drug alone) of the geometric means for the primary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for 'subjects' and 'treatment'. CIs will be calculated based on the residual error from the ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Period	Visit	Day	Planned time (relative to intake of drug cocktail[12] per visit) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Blood sample for PK of BI 730357 and metabolite	Blood sample for PK of drug Cocktail [13]	Safety laboratory [8]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
SCR	1	-21 to -1			Screening (SCR)[1]			A	x	x	x
Period 1 / Treatment R (Drug cocktail alone)	2	-1	-26:00	07:00	Ambulatory visit			B[7]			x
			-13:00	20:00	Admission to trial site			x[5]			x
		1	-2:00	07:00			x[2]		x[2]	x[2]	x[2]
			-1:30	07:30	Standardized breakfast						
			0:00	**09:00**	**Administration of drug cocktail** [12]						
			0:30	09:30			x				
			1:00	10:00			x				
			1:30	10:30			x			x	x
			2:00	11:00	240 mL fluid intake		x				
			3:00	12:00			x				
			4:00	13:00	240 mL fluid intake, thereafter lunch[9]		x				x
			6:00	15:00			x				
			7:30	16:30	Extended snack (voluntary)						
			8:00	17:00			x				
			10:30	19:30	Standardized dinner						
			12:00	21:00			x				x
		2	24:00	09:00	Breakfast[9]		x	C			x
			28:00	13:00	Lunch						
			31:30	16:30	Snack (voluntary)						
			34:30	19:30	Dinner[9]						x
		3	48:00	09:00			x	C		x	x
			48:05	09:05	Breakfast (voluntary), discharge from trial site						
		4	71:00	08:00	Ambulatory visit		x				x
		5	95:00	08:00	Ambulatory visit		x				x
		6	119:00	08:00	Ambulatory visit		x				x
		7	143:00	08:00	Ambulatory visit		x	B			x

Period	Visit	Day	Planned time (relative to intake of drug cocktail[12] per visit) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Blood sample for PK of BI 730357 and metabolite	Blood sample for PK of drug Cocktail [13]	Safety laboratory [8]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
Period 2 / Treatment T (Drug cocktail plus BI 730357)	3	-14	-338:30	06:30	Ambulatory visit, standardized breakfast [9]			x[11,2]	x[2]	x[2]	x[2]
			-338:00	07:00	**Administration of BI 730357**						
			-326:30	18:30	Ambulatory visit, standardized dinner [9]						x
			-326:00	19:00	**Administration of BI 730357**						
		-13	-314:30	06:30	Ambulatory visit, standardized breakfast [9]						x
			-314:00	07:00	**Administration of BI 730357**						
			-302:30	18:30	Ambulatory visit, standardized dinner [9]						x
			-302:00	19:00	**Administration of BI 730357**						
		-12	-290:30	06:30	Ambulatory visit, standardized breakfast [9]						x
			-290:00	07:00	**Administration of BI 730357**						
			-278:30	18:30	Ambulatory visit, standardized dinner [9]						x
			-278:00	19:00	**Administration of BI 730357**						
		-11	-266:30	06:30	Ambulatory visit, standardized breakfast [9]						x
			-266:00	07:00	**Administration of BI 730357**						
			-254:30	18:30	Ambulatory visit, standardized dinner [9]						x
			-254:00	19:00	**Administration of BI 730357**						
		-10	-242:30	06:30	Ambulatory visit, standardized breakfast [9]						x
			-242:00	07:00	**Administration of BI 730357**						
			-230:30	18:30	Ambulatory visit, standardized dinner [9]						x
			-230:00	19:00	**Administration of BI 730357**						
		-9	-218:30	06:30	Ambulatory visit, standardized breakfast [9]						x
			-218:00	07:00	**Administration of BI 730357**						
			-206:30	18:30	Ambulatory visit, standardized dinner [9]						x
			-206:00	19:00	**Administration of BI 730357**						
		-8	-194:30	06:30	Ambulatory visit, standardized breakfast [9]			B[2]	x[2]	x[2]	x[2]
			-194:00	07:00	**Administration of BI 730357**						
			-182:30	18:30	Ambulatory visit, standardized dinner [9]						x
			-182:00	19:00	**Administration of BI 730357**						
		-7	-170:30	06:30	Ambulatory visit, standardized breakfast [9]						x
			-170:00	07:00	**Administration of BI 730357**						
			-158:30	18:30	Ambulatory visit, standardized dinner [9]						x
			-158:00	19:00	**Administration of BI 730357**						
		-6	-146:30	06:30	Ambulatory visit, standardized breakfast [9]						x
			-146:00	07:00	**Administration of BI 730357**						
			-134:30	18:30	Ambulatory visit, standardized dinner [9]						x
			-134:00	19:00	**Administration of BI 730357**						
		-5	-122:30	06:30	Ambulatory visit, standardized breakfast [9]						x
			-122:00	07:00	**Administration of BI 730357**						
			-110:30	18:30	Ambulatory visit, standardized dinner [9]						x
			-110:00	19:00	**Administration of BI 730357**						
		-4	-98:30	06:30	Ambulatory visit, standardized breakfast [9]						x
			-98:00	07:00	**Administration of BI 730357**						
			-86:30	18:30	Ambulatory visit, standardized dinner [9]						x
			-86:00	19:00	**Administration of BI 730357**						
		-3	-74:30	06:30	Ambulatory visit, standardized breakfast [9]						x
			-74:00	07:00	**Administration of BI 730357**						
			-62:30	18:30	Ambulatory visit, standardized dinner [9]						x
			-62:00	19:00	**Administration of BI 730357**						

Period	Visit	Day	Planned time (relative to intake of drug cocktail[12] per visit) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Blood sample for PK of BI 730357 and metabolite	Blood sample for PK of drug Cocktail [13]	Safety laboratory [8]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
Period 2 / Treatment T (Drug cocktail plus BI 730357)	3	-2	-50:30	06:30	Ambulatory visit, standardized breakfast [9]						x
			-50:00	07:00	**Administration of BI 730357**						
			-38:30	18:30	Ambulatory visit, standardized dinner [9]						x
			-38:00	19:00	**Administration of BI 730357**						
		-1	-25:30	07:30	Ambulatory visit, standardized breakfast [9]						x
			-25:00	08:00	**Administration of BI 730357**	x[3]		B[3]			
			-14:00	19:00	Admission to trial site			x[2,5]			x[2,10]
			-13:30	19:30	standardized dinner [9]						
			-13:00	20:00	**Administration of BI 730357**	x[3]					
		1	-2:00	07:00					x[2]	x[2]	x[2]
			-1:30	07:30	Standardized breakfast [9]						
			-1:00	08:00	**Administration of BI 730357**	x[3]					
			0:00	**09:00**	**Administration of drug cocktail** [12]	x[3]	x[3]				x[3]
			0:30	09:30		x	x				
			1:00	10:00		x	x				
			1:30	10:30		x	x			x	x
			2:00	11:00	240 mL fluid intake	x	x				
			3:00	12:00		x	x				
			4:00	13:00	240 mL fluid intake, thereafter lunch[9]	x	x				x
			6:00	15:00		x	x				
			7:30	16:30	Extended snack (voluntary)						
			8:00	17:00		x	x				
			10:30	19:30	Standardized dinner [9]						x
			11:00	20:00	**Administration of BI 730357**	x[3]					
			12:00	21:00			x				
		2	22:30	07:30	Standardized breakfast [9]						x
			23:00	08:00	**Administration of BI 730357**	x[3]					
			24:00	09:00			x	C			
			28:00	13:00	Lunch						
			31:30	16:30	Extended snack (voluntary)						
			34:30	19:30	Standardized dinner [9]						x
			35:00	20:00	**Administration of BI 730357**	x[3]					
		3	46:30	07:30	Standardized breakfast [9]					x[2]	x[2]
			47:00	08:00	**Administration of BI 730357**	x[3]					
			48:00	09:00			x	C			
			48:05	09:05	Discharge from trial site						
			58:00	19:00	Ambulatory visit, standardized dinner [9]						x
			58:30	19:30	**Administration of BI 730357**						
		4	70:00	07:00	Ambulatory visit, standardized breakfast [9]						x
			70:30	07:30	**Administration of BI 730357**						
			71:00	08:00			x				
			82:00	19:00	Ambulatory visit, standardized dinner [9]						x
			82:30	19:30	**Administration of BI 730357**						
		5	94:00	07:00	Ambulatory visit, standardized breakfast [9]						x
			94:30	07:30	**Administration of BI 730357**						
			95:00	08:00			x				
			106:00	19:00	Ambulatory visit, standardized dinner [9]						x
			106:30	19:30	**Administration of BI 730357**						

Period	Visit	Day	Planned time (relative to intake of drug cocktail[12] per visit) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Blood sample for PK of BI 730357 and metabolite	Blood sample for PK of drug Cocktail [13]	Safety laboratory [8]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
2	3	6	118:00	07:00	Ambulatory visit, standardized breakfast [9]						x
			118:30	07:30	**Administration of BI 730357**						
			119:00	08:00			x				
			130:00	19:00	Ambulatory visit, standardized dinner [9]						x
			130:30	19:30	**Administration of BI 730357**						
		7	143:00	08:00	Ambulatory visit		x	B		x	x
FU	4	13 to 20			End of trial (EoTrial) examination[4]			D	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 pregnancy test in women and drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria, [redacted]
2. The time is approximate; the procedure is to be performed and completed within 2h prior to the next standardized breakfast or standardized breakfast indicated at the same time
3. The time is approximate; the procedure is to be performed within 15 min before the drug administration indicated at the same time
4. At the end of trial visit the EoTrial examination includes physical examination, vital signs, ECG, safety laboratory (including pregnancy test in women), recording of AEs and concomitant therapies, [redacted]
5. Only urine drug screening and alcohol breath test as well as pregnancy test in women will be done at this time.
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. Safety laboratory to be taken and to be medically evaluated prior to first administration of trial medication.
8. Letter A, B, C and D define different sets of safety laboratory examinations (see Section 5.2.3)
9. If several actions are indicated at the same time, the intake of meals will be the last action.
10. [redacted]
11. Only pregnancy test in women will be done at this time
12. Oral cocktail of CYP probe drugs consisting of caffeine, warfarin, omeprazole, and midazolam
13. PK sampling for drug cocktail includes sampling at the following planned times relative to administration of the cocktail with CYP probe drugs [h:min]:
    0 (within 2h predose), 0:30, 1:00, 1:30, 2:00, 3:00, 4:00, 6:00, 8:00, 12:00, 24:00 for omeprazole and midazolam,
    0 (within 2h predose), 0:30, 1:00, 1:30, 2:00, 3:00, 4:00, 6:00, 8:00, 12:00, 24:00, 48:00 for caffeine,
    0 (within 2h predose), 0:30, 1:00, 1:30, 2:00, 3:00, 4:00, 6:00, 8:00, 12:00, 24:00, 48:00, 71:00, 95:00, 119:00, 143:00 for warfarin.

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[redacted]

[redacted]

ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ALCOA	attributable, legible, contemporaneous, original, accurate (dimensions of data integrity)
ANOVA	Analysis of variance
AUC_{0-24}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 hours
AUC_{0-96}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 96 hours
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
BI	Boehringer Ingelheim
b.i.d.	*Bis in die* (twice a day)
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
C-SSRS	Columbia-Suicide Severity Rating Scale
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
CYP	Cytochrome P450
D	Day
DDI	Drug-drug interaction
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid

ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EoTrial	End of trial
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
gMean	Geometric mean
HPC	Human Pharmacology Centre
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IL	Interleukin
IPD	Important protocol deviation
IQRM	Integrated quality and risk management
IRB	Institutional Review Board
ISF	Investigator site file
λ_z	Terminal rate constant of the analyte in plasma
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple-rising dose
NOAEL	No observed adverse event level
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
PUVA	Psoralen ultraviolet A
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

$RAUC_{0-\infty,M/P}$	Ratio of metabolite $AUC_{0-\infty}$ to parent $AUC_{0-\infty}$
RCTC	Rheumatology Common Toxicity Criteria
REP	Residual effect period
RORγ	Retinoic acid-related orphan receptor γ (full length protein)
RORγt	Retinoic acid-related orphan receptor γt (splice variant of RORγ protein)
SAE	Serious adverse event
SCR	Screening
[redacted]	[redacted]
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SRD	Single-rising dose
ss	(at) steady state
T	Test product or test treatment
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set
t_z	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
UN	Unstructured
UNR	Unstructured correlation
V	Visit
V_z	Apparent volume of distribution during the terminal phase after intravascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
WOCBP	Woman of childbearing potential
XTC	Ecstasy

1. INTRODUCTION

BI 730357 is an antagonist of the retinoic acid-related orphan receptor (ROR)γt . It is being developed as an oral therapy for the treatment of patients with plaque psoriasis (PsO), as well as other Th17-mediated diseases. RORγt antagonism is a novel mechanism of action.

The trial will be performed to assess the influence of BI 730357 on the pharmacokinetics of caffeine (CYP1A2 probe drug), warfarin (CYP2C9 probe drug), omeprazole (CYP2C19 probe drug) and midazolam (CYP3A4 probe drug).

1.1 MEDICAL BACKGROUND

RORγt is a nuclear hormone receptor/transcription factor expressed in Th17 cells (i.e., a subset of T helper cells which produce interleukin 17, and other signalling molecules) and in distinct subsets of lymphoid cells, including natural killer cells, innate lymphoid cells, and γδ T cells. [redacted]

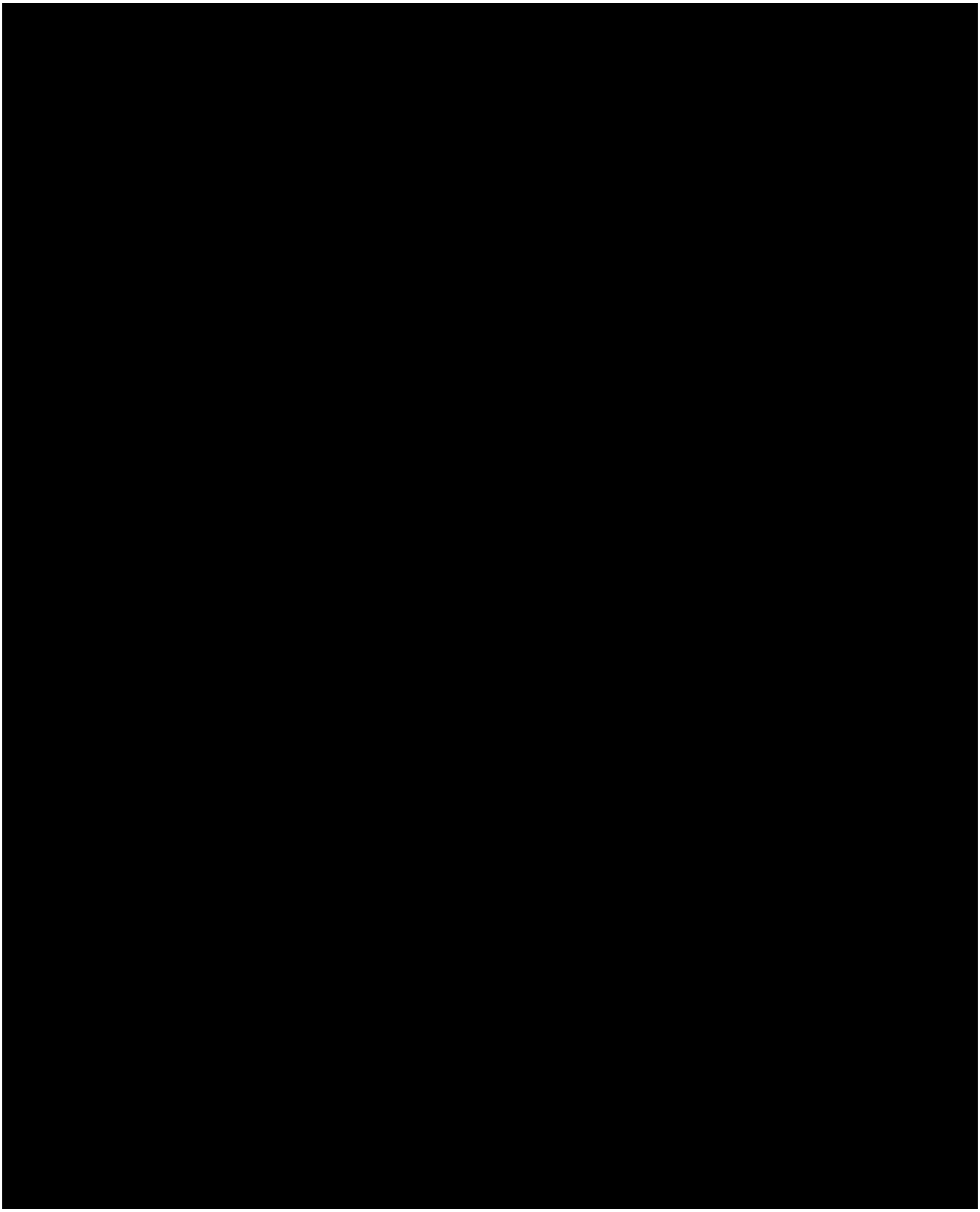
1.2 DRUG PROFILE

1.2.1 BI 730357

1.2.1.1 Nonclinical drug safety

General and safety pharmacology studies conducted with BI 730357 showed an acceptable profile for clinical trials. Please refer to the Investigator's Brochure (IB) [c09228382! "#$ %#$&#%()&*&-&*,-).

[redacted]



[redacted]

1.2.1.3 Clinical pharmacokinetics

In single rising dose (SRD) evaluation of BI 730357 administered to healthy male subjects, exposure to BI 730357 increased in a dose-proportional manner for solution between 2 and 8 mg and for tablet up to 50 mg, and thereafter increased in a less than dose-proportional manner, with approximately 1.5-fold increase in exposure with each 2-fold increase in dose, up to 400 mg in the fasted state. After administration of 800 mg BI 730357 under fed conditions, a maximum exposure of 77,900 nM*h (AUC_{0-inf}) and of 2,470 nM (C_{max}) was achieved. BI 730357 was cleared from plasma with a terminal half-life ranging from 20.0 to 29.8 hours after single dose administration. Exposure was 27% greater following administration of the 25 mg tablet under fed compared to fasted conditions, and continued to increase at higher doses with food, suggesting a positive food effect for BI 730357.

[redacted]

Following administration of multiple rising doses (trial 1407-0002), BI 730357 exposure increased in an approximately dose-proportional manner from 25 mg to 100 mg, and in a less than dose-proportional manner from 100 mg to 200 mg, in the fasted state. When administered in the fed state, higher BI 730357 plasma levels and exposures were observed, with a delayed peak in concentrations compared to fasted conditions. Median t_{max} values ranged from 1.00 to 2.75 hours in the fasted state, and increased to 2.55 to 4.00 hours in the

fed state. In the highest dose group of the MRD study (400 mg qd, fed conditions) a maximum exposure of 35,500 nM*h ($AUC_{\tau,ss}$) and of 2,210 nM ($C_{max,ss}$) was achieved.

Concentrations following multiple dosing appeared to be approximately double those following a single dose, with no relevant difference seen between 2- and 4-week profiles. Steady state was reached after approximately 7 days for all dose groups.

BI 730357 is a sensitive CYP3A substrate. Co-administration of itraconazole increased the exposure of BI 730357 by factor 9.3 ($AUC_{0-\infty}$) and 1.7 (C_{max}).

Administration of BI 730357 at doses of up to 400 mg once daily to healthy male subjects had no clinically-relevant effect on the pharmacokinetics of midazolam, a sensitive CYP3A substrate.

For a more detailed description of the BI 730357 PK profile, please refer to the current IB [c09228382].

1.2.1.4 Clinical safety in healthy subjects

Up to now, BI 730357 has been administered in 7 completed Phase I trials to more than 200 healthy subjects.

Trial 1407.1: In this trial, 66 subjects were exposed to BI 730357 (54 in the SRD part, 12 in the bioavailability (BA) part). In the SRD part, single doses from 8 mg to 800 mg were tested. Drug-related adverse events (AEs) were reported by 4 subjects on BI 730357 (3x headache, 1x oropharyngeal pain). These AEs were of mild or moderate (1 x headache) intensity and did not show any dose dependency. In the BA part no drug-related AEs were reported [c16462083].

Trial 1407-0002: This trial investigated the tolerability of BI 730357 after administration of multiple rising doses (25 mg to 400 mg) over 14 days. A total of 63 healthy subjects has been exposed to BI 730357. Among these 12 subjects reported drug-related AEs. These AEs were of mild or moderate intensity and did not show any dose dependency. Drug-related AEs reported by more than 1 subject comprise headache (4 subjects) and diarrhea (3 subjects). One subject in the 50 mg (fed) dose group developed a seborrhoic dermatitis on the 12th treatment day which lasted for 100 hours. This subject was not dosed on Day 13 and 14 and the AE was assessed to be not drug-related by the investigator [c25766034].

Trial 1407-0014: This trial investigated the effect of itraconazole on BI 730357 kinetics in 14 healthy subjects. For this purpose single doses of 50 mg BI 730357 have been administered with and without multiple doses of itraconazole. In the 'BI 730357 alone' period no drug-related AEs were reported. After combined administration of BI 730357 on

top of itraconazole, drug-related headache (mild) and nausea (moderate) were reported by one subject each [c27699953].

Trial 1407-0015: In this trial 18 Japanese healthy subjects were exposed to rising single doses of BI 730357 (50 to 200 mg). No drug-related AEs were reported [c27425119].

Trial 1407-0031: In this trial 6 healthy subjects were exposed to 50 mg C-14 labelled BI 730357. Mild headache was the only drug-related AE reported by one subject [c26494034].

Trial 1407-0032: This trial investigated the relative bioavailability of different solid oral formulations of BI 730357. For this purpose single doses of 50 mg (Part 1: 2 periods, 14 subjects), 100 mg (Part 3: 3 periods, 15 subjects) and 200 mg (Part 2: 2 periods, 14 subjects) were administered to healthy subjects. In Part 1 drug-related AEs comprised headache (4 cases) and diarrhea (1 case). In Part 2 drug-related headache was reported by 8 of 14 subjects. In Part 3 drug-related AEs comprised headache (2 cases) and nausea with vomiting (1 case). All drug-related AEs were of mild or moderate intensity [c28904523].

Trial 1407-0033: In this trial the absolute bioavailability of BI 730357 was investigated by administration of 50 mg tablets and 100 µg C-14 labelled BI 730357 given as intravenous microtracer to 6 healthy subjects. The only drug-related AE was an increased erection (mild) reported by 1 subject [c27700144].

For a more detailed description of the BI 730357 profile, please refer to the current IB [c09228382].

1.2.2 Compounds of the CYP probe cocktail

The potential induction or inactivation of the cytochrome P450 (CYP) isozymes CYP1A2, CYP2C9, CYP2C19 and CYP3A by BI 730357 will be investigated by the combined administration of the probe substrates caffeine, warfarin, omeprazole, and midazolam (partial [redacted] cocktail [P10-00100]).

All the substances of the [redacted] cocktail are approved drugs. For side effects and further details, please refer to the summaries of product characteristics of caffeine [R14-3265], warfarin [R18-2602], omeprazole [R20-1236], and midazolam [R19-1961].

A validation study has confirmed that the probe substrates of the [redacted] cocktail are safe and do not interact with each other when used in combination [P10-00100]. The [redacted] cocktail was designed to overcome potential disadvantages of other four- and five-probe cocktails [P04-02457]. In comparison with the well-known 'Cooperstown 5+1 cocktail' [P03-09924], intravenous midazolam was replaced by oral midazolam in order to reflect combined CYP3A activity in the intestine and liver, and dextromethorphan was substituted by metoprolol which appears to be a better CYP2D6 probe substrate with less intra-individual variability. Furthermore, the omeprazole dose could be reduced from 40 mg to 20 mg, and in contrast to mandatory co-administration of vitamin K1, the investigator has now the responsibility to monitor the necessity of administering the warfarin antidote. In the current trial, a partial [redacted] cocktail consisting of caffeine, warfarin, omeprazole, and midazolam is used. Metoprolol is omitted, as investigation of BI 730357 effects on CYP2D6 is not required.

1.2.2.1 Caffeine

Caffeine is the most-commonly used substance for CYP1A2 phenotyping. The first step in its metabolism is almost exclusively mediated by CYP1A2. Orally-administered caffeine is well absorbed by the small intestine within 45 minutes of ingestion, and then distributed throughout all tissues of the body. Peak blood concentrations are reached within 1 to 2 hours. Its volume of distribution is 0.52 to 1.06 L/kg. It has been shown that CYP1A2-mediated caffeine clearance accounts for more than 95% of overall caffeine elimination from plasma. In healthy adults, the elimination half-life of caffeine is 4 to 5 hours. Caffeine and its metabolites are predominantly eliminated by renal excretion [P05-10983, R06-0327, R14-1378].

1.2.2.2 Warfarin

Warfarin sodium is an anticoagulant which acts by inhibiting vitamin K-dependent coagulation factors [R18-2602]. Warfarin sodium is completely absorbed after oral administration with the peak concentration attained within the first 4 hours. Its volume of distribution is 0.12 L/kg. Orally-administered warfarin sodium is a racemic mixture of the R-and S-enantiomers. The half-life of R-warfarin sodium ranges from 37 to 89 hours, while that of S-warfarin sodium ranges from 21 to 43 hours. Approximately 80 to 85% of S-warfarin elimination occurs through 6- or 7-hydroxylation via CYP2C9. Thus, the PK of S-warfarin is used to quantify real-time CYP2C9 activity [R98-2274].

The anticoagulant effect generally starts within 24 hours after drug administration. However, peak anticoagulant effect may occur between 72 to 96 hours. The duration of action of a single dose of racemic warfarin is 2 to 5 days [R18-2602].

1.2.2.3 Omeprazole

Omeprazole is a proton pump inhibitor applied to treat ulcers, heartburn, gastroesophageal reflux, and Zollinger-Ellison syndrome [R20-1236]. The formation of 5-hydroxyomeprazole, the major primary metabolite of omeprazole, is dependent on CYP2C19 activity. In addition, omeprazole is metabolised by CYP3A to omeprazole sulphone. Since the affinity of omeprazole to CYP2C19 is 10 times higher than to CYP3A, omeprazole interferes with the metabolism of substrates for CYP2C19 but not of substrates for CYP3A [P96-3991]. Omeprazole has a small volume of distribution (0.3 L/kg). The plasma half-life is approximately 40 min. Plasma clearance was determined to be 0.3 to 0.6 L/min.

1.2.2.4 Midazolam

Midazolam is a short acting benzodiazepine which is used for the treatment of insomnia and as sedative premedication before surgical or diagnostic procedures. It has a volume of distribution of 0.7 to 1.2 L/kg at steady state. Its elimination half-life in young healthy volunteers ranges from 1.5 to 2.5 hours. The plasma clearance was determined to be 300 to 500 mL/min. Midazolam is almost completely eliminated by biotransformation to 1-hydroxymidazolam, and this process is mediated by CYP3A enzymes [R19-1961, R06-0294]. In contrast to testosterone or erythromycin, which have also been proposed as probes to monitor CYP3A activity, midazolam is metabolised specifically by CYP3A, and

does not serve as a substrate for other CYP450 isoenzymes or the drug transporter P-glycoprotein (P-gp). Intravenous midazolam is a sensitive *in vivo* probe of hepatic CYP3A activity, whereas orally-administered midazolam is metabolised by both intestinal and hepatic CYP3A.

1.2.3 Residual Effect Period

The Residual Effect Period (REP) of the cocktail is 9 days, referring to warfarin, the drug with the longest half-life among the cocktail components. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

The Residual Effect Period (REP) of BI 730357 is 7 days. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Drug-drug interactions (DDI) are complex and have proven to be a major challenge for health care providers. One of the questions that must be addressed before new drugs can be safely administered is whether there is a drug interaction with other medications taken by the patient for the treatment of co-morbidities. Therefore the interaction potential of a new compound is regularly evaluated during clinical drug development.

Based on *in vitro* data, BI 730357 and its metabolite CD 6975 are potential inducers of CYP1A2, CYP2C9, CYP2C19, and CYP3A4 at anticipated human therapeutic exposure levels. However, the predictive value of *in vitro* data is limited, and the probability of DDIs can entirely be assessed only with *in vivo* data in humans. [redacted]

Therefore, this trial is aimed to investigate the influence of BI 730357 and its metabolite on the activity of CYP1A2, CYP2C9, CYP2C19, and CYP3A by using *in vivo* probe drugs recommended by both the FDA [P12-05791] and EMA [P15-06991] as sensitive substrates for the respective CYP enzymes and that do not interact among each other when administered together.

Results of this DDI trial will provide for a general signal of potentially important DDI upon which further exploration can be based.

1.4 BENEFIT - RISK ASSESSMENT

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation, however, is of major importance for the development of BI 730357, which may help to treat patients with PsO or other Th-17 related diseases. Subjects are exposed to risks of study procedures and risks related to the exposure to the trial medication.

1.4.1 Procedure-related risks

The use of an indwelling venous catheter or venepuncture for, e.g., blood sampling may result in mild bruising, and in rare cases, in transient inflammation of the wall of the vein, or

nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period.

ECG electrodes may cause local and typically transient skin reactions.

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

1.4.2 Drug-related risks and safety measures

1.4.2.1 BI 730357

As the nature of the target and the mechanism of action of BI 730357 are well understood from pre-clinical studies, comparable compounds have been tested by other companies before, and the animal models are believed to be predictive for the effects in humans, BI 730357 is not seen as a high-risk compound.

Up to the present, BI 730357 has been administered to more than 200 healthy subjects. In these trials BI 730357 has been well tolerated. The most frequent drug-related AE is headache (in single trial parts up to 25-50% of exposed subjects reported drug-related headache). Further drug-related events that have been reported by more than one subject so far comprise diarrhea and nausea. All drug-related AEs were of mild or moderate intensity (see Section 1.2.1.4). Specific changes of laboratory values, vital signs or ECG parameters have not been described so far.

In the highest dose group of the MRD trial 1407-0002, 400 mg BI 730357 were administered over 28 days. This resulted in a mean exposure of 2,210 nmol/l ($C_{max,ss}$) and 35,500 nmol/l*h ($AUC_{\tau,ss}$), which was well tolerated by healthy subjects. In this trial, 300 mg *b.i.d.* will be administered over 20 days to healthy volunteers. Corresponding to model-based simulated medians (and 95% confidence intervals), the expected exposure of this dosing regimen is for $C_{max,ss}$ 4,130 nmol/l (3,530; 4,710) and for $AUC_{\tau,ss}$ 82,700 nmol/L*h (71,500; 93,900), which exceeds the exposure of the highest MRD dose group by factor 1.9 (C_{max}) and 2.3 (AUC). The expected exposure is about 62% (C_{max}) and 65% (AUC) of the NOAEL-exposure (6,600 nmol/l for C_{max} and 127,400 nmol/L*h for AUC_{0-24}) seen in the 4-week dog study (see Section 1.2.1.1).

In the SRD trial 1407.1, the administration of 800 mg BI 730357 under fed conditions resulted in an exposure of 2,470 nmol/L (C_{max}) and 77,900 nmol/L*h ($AUC_{0-\infty}$), which was well tolerated by healthy subjects.

Since preclinical data indicate that BI 730357 has phototoxicity potential, direct exposure to the sun or exposure to solarium radiation is not allowed during the entire study, and use of sunscreens is mandatory in that time (see Section 4.2.2.2).

As with other immune-targeted therapies, impaired host defense is a theoretical target-related toxicity, potentially resulting in increased risk of infection and/or malignancy. Th17 cells play an important role in defense against extracellular bacteria and fungi at mucosal surfaces [R16-3166, R16-3149]. IL-17 antagonists are associated with increased infections [R13-2643]. Homozygous, but not heterozygous RORγ knockout mice have a high incidence of T-cell lymphoma, thought to originate in the thymus [R16-2630]. While the translatability

of the knockout phenotype to pharmacological RORγ antagonism and to humans is unknown, this raises the hypothetical concern for clinical T-cell lymphoma risk. The exact cause of T-cell lymphomas in RORγ knockout mice is not fully understood, but changes in homeostasis in the thymus, such as thymocyte apoptosis and proliferation, are thought to play a role. AEs and SAEs consistent with malignancy, and specifically those representing lymphoma, are to be carefully monitored and evaluated throughout the BI 730357 clinical development program. Based on the data obtained with BI 730357 so far, the increased risk of infection and/or malignancy is considered to be extremely small.

Currently, information about the immune response in patients with SARS-CoV-2 infection is sparse and inconclusive. In severe cases of COVID-19, morbidity associated with SARS-CoV-2 infection may be attributed to immune activation and inflammation, with high levels of pro-inflammatory cytokines activated by RORγt. To date, there is no reliable evidence suggesting a link between the inhibition of the RORγt pathway and susceptibility to SARS-CoV-2 infections. Nonetheless, as with other immunomodulatory treatments, BI 730357 may potentially increase the risk of infections in healthy volunteers participating in clinical trials. Therefore, several risk mitigation measures (e.g., repeated laboratory tests for SARS-CoV-2 infection, exclusion of subjects with a history or findings indicative of a SARS-CoV-2 infection, close monitoring of AEs) are considered for this clinical trial. Trial conduct and protocol-defined procedures do not impose additional risk to trial participants. To address potential risks associated with operational aspects related to the participation in clinical trials in the context of the COVID-19 pandemic, different risk mitigation measures are considered based on local requirements and development of the pandemic. Any subject with suspected or diagnosed SARS-CoV-2 infection should be treated according to standard of care, and discontinuation of trial medication should be considered.

[redacted]

Considering the good tolerability of BI 730357 observed so far in healthy subjects and taken into account the planned safety measures (two cohorts, twice daily visits in the outpatient phase of BI 730357 dosing, safety lab, vital signs and ECG monitoring) no undue risk to healthy subjects is expected from participation in this study.

1.4.2.2 Caffeine

Caffeine has a large therapeutic window. Fluvoxamine, a potent inhibitor of CYP1A2, caused a 5-fold increase of caffeine-AUC in healthy subjects, but no side effects attributed to the intake of caffeine have been reported [P14-11944]. Comparable to this trial, a dose of 100 mg caffeine has been used. In contrast to fluvoxamine, BI 730357 is expected to be an inducer of CYP1A2. Therefore an undue safety risk to healthy subjects cannot be expected from potential BI 730357 interaction with caffeine.

Smoking and contraceptive steroids are known inducers and inhibitors of CYP1A2, respectively [P12-05791]. Subjects currently smoking or ex-smokers who quit smoking less than 30 days prior to screening examination, as well as subjects using hormonal

contraceptives or hormonal replacement therapy less than 30 days before the first administration of trial medication will be excluded from participation in this trial for potential interaction via CYP1A2.

1.4.2.3 Warfarin

The selected dose of 10 mg warfarin is commonly used as loading and maintenance dose during oral anticoagulation therapy, and is lower than the dose range (20-30 mg) which often has been used in DDI studies in the past. Following single dose administration, the anticipated bleeding risk of 10 mg warfarin is considered to be low. In previous DDI trials with warfarin, prothrombin time and INR values remained inside the reference ranges after single doses of 10 mg warfarin [U09-1674-04, c03142665] or increased up to 2-times upper normal limit at 36 h to 56 h after single dose administration of 25 mg warfarin [U10-2984-01].

The effect of warfarin on the production of vitamin K-dependent coagulation factors can be easily monitored by means of laboratory tests and clinical observation, and antagonised by administration of vitamin K1. This trial includes safety laboratory before and after each warfarin administration. In case of excessive anticoagulation, further warfarin treatment should be avoided. Considering the fact that BI 730357 is expected to be an inducer of CYP2C9, co-administration of BI 730357 may reduce warfarin exposure. Therefore, safety risks to healthy subjects resulting from warfarin administration are unlikely in this study.

1.4.2.4 Omeprazole

The therapeutic standard dose of omeprazole is 20 mg to 40 mg daily. In the treatment of Zollinger-Ellison syndrome, daily doses of up to 80 mg may be required. Omeprazole has a large therapeutic window. Fluvoxamin, a potent inhibitor of CYP2C19, caused a 4.5 fold increase of omeprazole exposure in healthy subjects (P14-11944). No side effects attributed to the intake of omeprazole have been reported by the authors. Comparable to this trial, doses of 20 mg omeprazole have been used.

Considering the fact that BI 730357 is expected to be an inducer of CYP2C19, co-administration of BI 730357 and omeprazole may reduce omeprazole exposure. Therefore, an undue safety risk to healthy subjects cannot be expected from omeprazole intake in this trial.

1.4.2.5 Midazolam

The administration of an oral dose of 2 mg midazolam is without a major sedative effect [P10-00100]. The therapeutic dose of midazolam is 7.5 mg to 15 mg. Considering the fact that BI 730357 may act as an inactivator of CYP3A4, the chosen dose of 2 mg provides a sufficient safety margin. The subjects will be kept in-house at the trial site for 48 hours after dosing, covering the full elimination of midazolam.

Furthermore, the potential inactivation of CYP3A4 is expected to be outweighed by a concurrent induction effect on CYP3A. In MRD trial 1407-0002 (see Section 1.2.1.3 and 1.2.1.4), the exposure of midazolam, a sensitive CYP3A4 substrate, was not impacted by BI 730357 doses of up to 400 mg *q.d.* administered under fed conditions (BI 730357 $C_{max,ss}$ of 2,210 nM) [c09228382].

If the net effect of BI 730357 should be an induction of CYP3A4, the midazolam exposure after administration of 2 mg will be reduced. Therefore, no undue safety risk to healthy subjects is expected from potential BI 730357 interaction with midazolam.

1.4.2.6 Drug-induced liver injury

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

1.4.2.7 Safety measures

For safety measures and assessments in detail, such as screening examination, AE/CT questioning, laboratory examinations, in-house periods, daily outpatient visits, ECG/vital signs measurements, or assessment of SIB, refer to the Flow Chart and Section 5.2. The safety measures are adequate to address the potential risks of the trial drugs to the volunteers.

1.4.3 Overall assessment of benefit-risk ratio

BI 730357 is a novel RORγt antagonist that has been adequately characterised in pre-clinical studies. Non-clinical BI 730357 safety data demonstrated an acceptable profile to support clinical trials in males and females, including women of childbearing potential. [redacted] This trial is required for the development of BI 730357. The resulting data are used to inform concomitant medication restrictions in planned patient trials.

Under consideration of their properties, all four probe substrates of the trial (caffeine, warfarin, omeprazole, and midazolam) are appropriate for phenotyping drug-metabolizing enzymes, are safe to use alone and in combination [P10-00100, P03-09924, P10-05867], and have, with exception of warfarin, a very large therapeutic window.

All doses chosen were based on the clinical tolerability of the probe drugs and the ability to assess reliable PK parameters. Taken together, there is no relevant risk arising from potential inactivation of metabolism of the probe substrates. Inactivation of enzymes is fully reversible once the interacting agent is discontinued. In case BI 730357 would induce CYP isoenzymes, this effect would lead to a decrease in exposure of probe drugs in Visit 3 and is therefore not increasing the risk.

The trial design is optimised to collect as much and as relevant information as possible on the inhibition and induction potential of BI 730357 without exposing participating volunteers to undue risk. However, there is always the potential of serious AEs (SAEs) occurring with intake of trial medication. Safety will be ensured by monitoring the subjects during

treatments on a once daily or twice daily basis under the supervision of a physician, which includes hospitalisation periods during administration of probe substrates as well as regular laboratory and clinical assessments and verbal communication about AEs. If the investigator should have any clinical concern, the safety of the subjects will be of paramount importance. The investigator will have the discretion to remove subjects from the trial should there be any safety concerns or if the subject's wellbeing is at jeopardy.

Previously, a comparable cocktail study was performed at the trial site with another investigational product. In this trial, the probe drugs midazolam (2 mg), warfarin (10 mg), omeprazole (20 mg), metoprolol (50 mg), caffeine (100 mg), and digoxin (0.25 mg) (full [redacted]Cocktail + digoxin) were well tolerated by the subjects [c03142665].

Overall, considering the good tolerability of BI 730357 observed so far in healthy subjects and in patients, the sponsor feels that the benefit of a successful development of BI 730357 outweighs the potential risks to healthy participants.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to assess the influence of multiple doses of BI 730357 on single dose kinetics of cytochrome P450 (CYP) probe substrates, as a means of predicting drug-drug interactions. These probe drugs substrates are caffeine (for CYP1A2), warfarin (for CYP2C9), omeprazole (for CYP2C19), and midazolam (for CYP3A).

2.1.2 Primary endpoints

The following primary endpoints will be determined for the probe drugs caffeine, warfarin (specifically S-warfarin), omeprazole, and midazolam when administered without BI 730357 and when co-administered with BI 730357 at BI 730357 steady-state:

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

2.1.3 Secondary endpoint

Not applicable.

[redacted]

[redacted]

2.2.2.2 Safety and tolerability

Safety and tolerability of BI 730357 and the probe drugs will be assessed based on:

- AEs (including clinically-relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure, pulse rate)
- [redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This trial is designed to assess the effects of BI 730357 on the activity of CYP1A2, CYP2C9, CYP2C19, and CYP3A, by utilizing a cocktail of probe drugs which contains specific substrates for these CYP enzymes. The trial will assess long-term effects of BI 730357 on CYP enzymes after achievement of steady-state levels of BI 730357 and after adaptation of CYP enzyme levels following continuous administration of BI 730357.

The trial will be performed as an open-label, two-treatment, two-period fixed sequence design trial in healthy male and female subjects enrolled at a single site. Sixteen subjects will receive the following oral treatments (for details refer to Section 4.1.):

Reference Treatment R (Trial Visit 2)

- 100 mg caffeine, 10 mg warfarin, 20 mg omeprazole, and 2 mg midazolam together as cocktail and single dose in the morning of Day 1 of Visit 2

Test treatment T (Trial Visit 3)

- 100 mg caffeine, 10 mg warfarin, 20 mg omeprazole, and 2 mg midazolam together as cocktail and single dose in the morning of Day 1 of Visit 3 (1 hour after the morning dose of BI 730357)
- 300 mg BI 730357 as multiple dose every 12 hours over 20 days in the morning and evening on Day -14 to Day 6 of Visit 3

There will be an interval of at least 20 days between the single-dose administrations of the cocktail on Day 1 of Visit 2 and on Day 1 of Visit 3.

For a single subject the schedule of trial participation can be displayed as follows:

- Screening examination (Visit 1): up to 21 days
- Treatment period 1 (Visit 2): 7 days
- Treatment period 2 (Visit 3): 20 days
- EoTrial examination (Visit 4): up to 13 days

Considering the flexible time frame for screening and follow-up examination the expected total trial duration for a single subject is about 6-9 weeks.

The trial population will be divided into 2 cohorts. The first cohort should not contain more than 6 subjects. The dosing of the 2nd cohort will start at the earliest 6 days after starting the dosing in the preceding first cohort.

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

A schematic diagram of the trial design is displayed in Figure 3.1: 1 below.

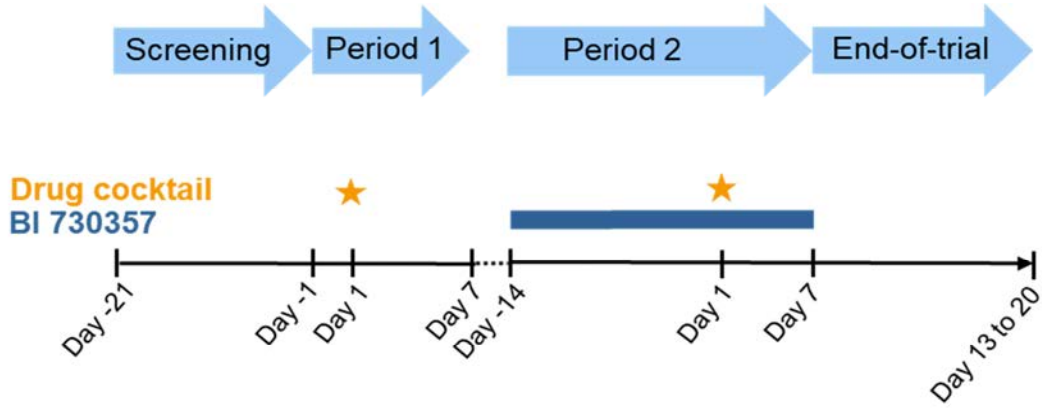


Figure 3.1: 1 Trial design

The drug cocktail consists of 100 mg caffeine, 10 mg warfarin, 20 mg omeprazole and 2 mg midazolam, administered as single oral dose on Day 1 of Period 1 and Period 2. Twice daily doses of 300 mg BI 730357 will be administered from Day -14 to Day 6 of Period 2.

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

For PK trials comparing different treatments, the crossover design is preferred because of its efficiency: since each subject serves as his own control, the comparison between treatments is based on an intra-subject comparison, thus removing inter-subject variability from the comparison between treatments [R94-1529].

Because of the long half-life of BI 730357 and its metabolite and its suspected induction potential on various cytochrome enzymes and to avoid overlapping inhibitory effects, a two-period fixed sequence design was selected, with administration of BI 730357 in the second treatment period (Visit 3) only. This design is not expected to lead to systematic errors in the estimation of the treatment effects, since nonspecific time-effects are unlikely due to the short trial duration.

All probe drugs used in this trial are listed as sensitive *in vivo* probes for drug-drug interaction trials by both the FDA [P12-05791] and EMA [P12-10638].

Caffeine, warfarin, omeprazole and midazolam, are components of the validated [redacted] cocktail [P10-00100]. The cocktail approach is an effective way to assess the drug-drug interaction (DDI) potential of development compounds that are expected (based on preclinical data) to affect more than one metabolic pathway or are potential gene inducers. A great advantage of the cocktail approach is the reduced number of subjects that will be exposed to the development compound (as perpetrator drug) compared to single DDI studies [P04-02212]. In these cases the performance of so called cocktail studies is accepted by regulatory authorities (P12-05791, P12-10638).

A dosing duration of seven days is adequate to ensure achievement of PK steady state of BI 730357, and further seven days to cover transient metabolic effects (e.g. induction of CYPs 1A2, 2C9, 2C19, or 3A) that may affect the PK of the probe drug substrates.

For this PK drug-drug interaction trial, open-label treatment is acceptable, because the primary and secondary endpoints of this trial are PK endpoints derived from measurement of plasma concentrations of BI 730357. These endpoints are not expected to be affected by knowledge of treatment.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 16 healthy subjects (if feasible at least 4 of each sex) will enter the study. They will be recruited from the volunteers' pool of the trial site.

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

3.3.1 Main diagnosis for trial entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 55 years (inclusive)
3. BMI of 18.5 to 29.9 kg/m^2 (inclusive)
4. Signed and dated written informed consent prior to admission to the study, in accordance with GCP and local legislation
5. Either male subject, or female subject who meet any of the following criteria from at least 30 days before the first administration of trial medication until 30 days after trial completion:
   - Use of non-hormonal intrauterine device plus condom for birth control
   - A vasectomised sexual partner (vasectomy at least 1 year prior to enrolment)
   - Surgically sterilised (including hysterectomy or bilateral tubal occlusion)
   - Postmenopausal, defined as at least 1 year of spontaneous amenorrhea (in questionable cases a blood sample with levels of FSH above 40 U/L and estradiol below 30 ng/L is confirmatory)

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR, or ECG) deviating from normal and assessed as clinically relevant by the investigator

2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 45 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological, or hormonal disorders
6. Cholecystectomy or other surgery of the gastrointestinal tract (except appendectomy or simple hernia repair) that could interfere with the PK of the trial medication
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
12. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
13. Current smoker or ex-smoker who quit smoking less than 30 days prior to screening examination
14. Use of nicotine replacement devices within 2 weeks prior to first administration of trial medication or during the trial
15. Alcohol abuse (consumption of more than 12 g per day for females and 24 g per day for males)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
18. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
19. Inability to comply with the dietary regimen of the trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males or repeatedly greater than 470 ms in females) or any other relevant ECG finding at screening

21. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the trial
23. Subjects who, in the investigator's judgement, are perceived as having an increased risk of bleeding, for example because of:
    - haemorrhagic disorder or bleeding diathesis,
    - trauma or surgery within the last 4 weeks or as long as an excessive risk of bleeding persists after these events,
    - planned surgery during trial participation,
    - history of arteriovenous malformation or aneurysm,
    - history of gastroduodenal ulcer disease or gastrointestinal haemorrhage, or
    - history of intracranial, intraocular, spinal, retroperitoneal, or atraumatic intraarticular bleeding
24. Within 10 days prior to administration of trial medication, use of any drug that could affect blood coagulation (e.g., acetylsalicylic acid, heparin)
25. Thrombocytopenia (platelet count less than 100 /nL) or low haemoglobin count (haemoglobin less than 11.6 g/dL for females and 13.5 g/dL for males) at screening
26. Any lifetime history of suicidal behaviour (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour)
27. Any suicidal ideation of type 2 to 5 on the C-SSRS in the past 12 months (i.e. active suicidal thought without method, intent or plan; active suicidal thought with method but without intent or plan; active suicidal thought with method and intent but without specific plan; or active suicidal thought with method, plan and intent)
28. For female subjects:
    - positive pregnancy test, pregnancy, or plans to become pregnant within 30 days after study completion,
    - concomitant use of hormonal replacement therapy or hormonal contraceptives,
    - lactation period
29. During COVID-19 pandemic: laboratory test indicative of an ongoing SARS-CoV-2 infection

For study restrictions, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

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

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

3.3.4.1 Discontinuation of trial treatment

An individual subject must be withdrawn by the investigator from trial treatment if any of the following discontinuation criteria apply:

1. The subject wants to discontinue trial treatment, without the need to justify the decision
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as pregnancy, surgery, adverse events [AEs], or diseases)
5. The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF
6. [redacted]

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

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

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial at any time for any of the following reasons (no. 2 is mandatory discontinuation criterion):

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. New toxicological findings, SAEs, or any safety information invalidating the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects have drug-related and clinically-relevant AEs of moderate or severe intensity, or if at least 1 drug-related SAE is reported
3. Violation of GCP or the CTP impairing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product

3.3.5 Replacement of subjects

In case more than 4 subjects do not complete the trial (including non PK-evaluable subjects), the Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational product BI 730357 will be provided by BI Pharma GmbH & Co. KG, Germany. Caffeine, warfarin, omeprazole, and midazolam will be obtained from a public pharmacy.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the trial products are given below:

Trial product 1 (CYP1A2 probe substance)

Brand Name:	Percoffedrinol® N 50 mg Tabletten
Substance:	Caffeine
Pharmaceutical formulation:	Tablet
Source:	[redacted]
Unit strength:	50 mg
Posology:	2 – 0 – 0
Route of administration:	Oral
Duration of use:	Single dose on Day 1 of Visits 2 and 3 (2 days in total)

Trial product 2 (CYP2C9 probe substance)

Brand Name:	Coumadin® 5 mg
Substance:	Warfarin sodium
Pharmaceutical formulation:	Tablet
Source:	[redacted]
Unit strength:	5 mg
Posology:	2 – 0 – 0
Route of administration:	Oral
Duration of use:	Single dose on Day 1 of Visits 2 and 3 (2 days in total)

Trial product 3 (CYP2C19 probe substance)

Brand Name:	Antra MUPS® 20 mg magensaftresistente Tabletten
Substance:	Omeprazole
Pharmaceutical formulation:	Gastro-resistant tablet
Source:	[redacted]
Unit strength:	20 mg
Posology:	1 – 0 – 0
Route of administration:	Oral
Duration of use:	Single dose on Day 1 of Visits 2 and 3 (2 days in total)

Trial product 4 (CYP3A4 probe substance)

Brand Name:	Midazolam-ratiopharm® 2 mg/mL orale Lösung
Substance:	Midazolam
Pharmaceutical formulation:	Oral solution
Source:	[redacted]
Unit strength:	2 mg/mL
Posology:	1 mL – 0 – 0
Route of administration:	Oral
Duration of use:	Single dose on Day 1 of Visits 2 and 3 (2 days in total)

Trial product 5 (BI investigational product)

Substance:	BI 730357
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	100 mg
Posology:	3 – 0 – 3
Route of administration:	Oral
Duration of use:	Multiple doses from Day -14 to Day 6 of Visit 3 (20 days in total)

4.1.2 Selection of doses in the trial

Single doses of caffeine 100 mg, warfarin 10 mg, omeprazole 20 mg, and midazolam 2 mg are standard doses used in clinical DDI trials. The doses were selected based on their tolerability and the ability to show a PK interaction if present. For caffeine, 100 mg was chosen as it is approximately the amount of caffeine in one cup of coffee. For warfarin, 10 mg is commonly used as starting and maintenance dose for oral anticoagulation. For omeprazole, a dose of 20 mg once a day is used in the treatment of symptomatic gastro-oesophageal reflux disease and duodenal ulcer. For midazolam, an oral dose of about 2 mg should lead to significant systemic exposure without major sedative effect [P10-00100].

According to DDI-guidelines, the exposure of the offender drug should be similar to the exposure seen under clinical conditions in patients. [redacted]

4.1.3 Method of assigning subjects to treatment groups

There is only one treatment sequence investigated in this trial, and each subject will be allocated to the same treatment sequence (R-T). The subjects will be allocated to a trial subject number by drawing lots prior to first administration of trial medication. Once a subject number has been assigned, it cannot be reassigned to any other subject.

Reference and test treatments will be administered in the sequence specified in the Flow Chart.

4.1.4 Drug assignment and administration of doses for each subject

This trial is a two-period fixed sequence design trial. All subjects will receive BI 730357 and probe drugs in a fixed order. The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substances	Formulation, Regimen	Unit Strength (mg)	Number of units/volume administered	Total Daily Dose (mg)	Study Visit (V), Day (D)
Reference (R)	Caffeine	tablet, *q.d.*	50	2 tablets	100	V2, D1
	+ Warfarin	tablet, *q.d.*	5	2 tablets	10	V2, D1
	+ Omeprazole	tablet, *q.d.*	20	1 tablet	20	V2, D1
	+ Midazolam	oral solution, *q.d.*	2/mL	1 mL	2	V2, D1
Test (T)	BI 730357	tablet, *b.i.d.*	100	3 tablets	600	V3, D-14 to D6
	Caffeine	tablet, *q.d.*	50	2 tablets	100	V3, D1
	+ Warfarin	tablet, *q.d.*	5	2 tablets	10	V3, D1
	+ Omeprazole	tablet, *q.d.*	20	1 tablet	20	V3, D1
	+ Midazolam	oral solution, *q.d.*	2/mL	1 mL	2	V3, D1

The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in a standing position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g., reconstitution), if correct dosage cannot be ensured otherwise.

At each dosing occasion the trial medication should be administered within 2 minutes. The liquid and oral components of the CYP probe cocktail should be administered in the same order for all subjects.

The cocktail administrations will be separated by a wash-out of at least 20 days.

A standardised meal (1 bread roll with 15 mg butter, sliced cheese and sliced sausage, and a cup of water or decaffeinated coffee without sugar) will be served 30 min before each BI 730357 administration. The standardized meals must be completely consumed prior to drug administration. To assure comparable conditions for the cocktail administration, the

standardised meal will also be served 90 min before the planned dosing of the CYP probe cocktail of reference treatment R. All meals are to be consumed within 30 minutes.

Subjects will be kept in-house under close medical surveillance until 48 hours following administration of the CYP-probe cocktail (containing caffeine, warfarin, omeprazole, and midazolam).

During the first 4 hours after administration of the CYP-probe cocktail on Day 1, and the first 2 hours after all other trial drug administrations, subjects are not allowed to lie down (i.e., no declination of the upper body of more than 45 degrees from upright posture), except for medical reasons or for recording of 12-lead ECG and vital signs measurements.

For restrictions with regard to diet, see Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

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

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

4.1.6 Packaging, labelling, and re-supply

BI 730357

BI 730357 tablets will be provided by BI. They will be packaged and labelled in accordance with local law and the principles of Good Manufacturing Practice. For details of packing and the description of the label, refer to the ISF.

The telephone number of the sponsor and the name, address, and telephone number of the trial site are provided in the subject information form. The EudraCT number is indicated on the title page of this protocol as well as on the subject information and informed consent forms.

No re-supply is planned.

Caffeine, warfarin, omeprazole, and midazolam

Caffeine, warfarin, omeprazole, and midazolam will be obtained as commercial products by the clinical trial site from a public pharmacy. The drug will be dispensed out of the original, unmodified packages.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area in accordance with the recommended (labelled) storage conditions. If necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, the Clinical Trial Manager (as provided in the list of contacts) is to be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered from the sponsor following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee
- Approval/notification of the regulatory authority, e.g., competent authority
- Availability of the *curriculum vitae* of the Principal Investigator
- Availability of a signed and dated clinical trial protocol

Only authorised personnel documented in the form 'Trial Staff List' may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the disposal of unused products.These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to trial subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of disposal of remaining trial medication, the investigator or designee must verify that no remaining supplies are in the investigator's possession.

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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

No bleeding events are expected in this trial, as warfarin is given as a single dose. In case of excessive anticoagulation with or without bleeding, further warfarin administration should be avoided and if necessary treated by administration of oral or parenteral vitamin K_1. In case of minor bleeding, 5 to 10 mg vitamin K_1 may be given as a single oral dose. If minor bleeding progresses to major bleeding, give 10 to 20 mg (rarely up to 50 mg) parenteral vitamin K_1. In emergency situations of severe haemorrhage, clotting factors can be returned to normal by administering 200 to 500 mL of fresh whole blood or fresh frozen plasma, or by giving commercial prothrombin complex concentrate.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

Known inhibitors/inducers of CYPs 1A2, 2C9, 2C19, or CYP3A should be avoided during the entire trial. Particularly, hormonal oral contraceptives, hormonal replacement therapy, and nicotine replacement devices are not allowed due to potential for CYP1A2 inhibition.

4.2.2.2 Restrictions on diet and life style

Poppy seed-containing foods should not be consumed starting 3 days before the first drug administration in each treatment period, in order to avoid false-positive results in the drug screen.

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

No food is allowed within 10 hours before and 4 hours after intake of the CYP probe cocktail (except breakfast served 90 minutes before administration).

Subjects will be advised to not consume any food within 2 hours before and 1 hour after administration of BI 730357 other than the meals provided at the site before drug intake.

On PK profile days (Day 1 of Visits 2 and 3), from 1 hour before drug intake until lunch, fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water at 2 and 4 hours after intake of the CYP probe substrates (mandatory for all subjects). From lunch until dinner, total fluid intake is restricted to 2000 mL on these days. Outside these times, water and fluids, which are not excluded for this trial (see succeeding sentences), may be consumed ad libitum.

Green tea, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products containing St. John's wort (*Hypericum perforatum*) are not permitted from 7 days before the first administration of trial medication in Visit 2 until after the last PK sample of Visit 3 is collected.

Alcoholic beverages are not permitted from 2 days before the first administration of trial medication in Visit 2 until after the last PK sample in Visit 3 is collected.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed within 12 hours before and during the in-house confinement at the trial site.

Smoking is not allowed starting from 30 days prior to screening until EoTrial examination.

Excessive physical activity (such as competitive sport) should be avoided during the entire trial, starting with the screening examination until the end of trial examination.

Direct exposure to the sun or exposure to solarium radiation, treatment with ultraviolet light (e.g., PUVA), or medication with known phototoxicity potential (e.g., doxycycline) should be

avoided from the first administration of trial medication until the EoTrial examination. The use of sunscreens is mandatory in that time.

If female subjects of child-bearing potential are included, adequate contraception is to be maintained throughout the course of the trial (see Section 3.3.2 for adequate measures).

4.3 TREATMENT COMPLIANCE

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

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (results of alcohol history not mandatory to be entered into CRF or to be reported), relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, physical examination, and assessment of suicidal ideation and behaviour using the C-SSRS ('baseline/screening scale'). At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, physical examination, [redacted]

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) will be measured by a blood pressure monitor (Dinamap Pro 100, [redacted]) at the times indicated in the Flow Chart, after subjects have rested for at least 5 minutes in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in the Flow Chart after the subjects have fasted for at least 10 hours. For retests, at the discretion of the investigator or designee, overnight fasting is not required. The same applies to time points scheduled after breakfast.

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

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

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A[1]	B[1]	C[1]	D[1]
Haematology	Haematocrit	X	X	--	X
	Haemoglobin	X	X	--	X
	Red Blood Cell Count/Erythrocytes	X	X	--	X
	White Blood Cells/Leukocytes	X	X	--	X
	Platelet Count/Thrombocytes (quant)	X	X	--	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X	--	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X	--	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs)/Leukocytes; Neut. Poly (segs), absol.; Neutrophils Bands/Leukocytes; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.				
Coagulation	Activated Partial Thromboplastin Time	X	X	X	X
	Prothrombin time	X	X	X	X
	Prothrombin time - INR (International Normalization Ratio)	X	X	X	X
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	X	X	--	X
	ALT [Alanine transaminase] /GPT, SGPT	X	X	--	X
	Alkaline Phosphatase	X	X	--	X
	Gamma-Glutamyl Transferase	X	X	--	X
	Creatine Kinase [CK]	X	--	--	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	--	--	X
Hormones	Thyroid Stimulating Hormone	X	--	--	--
Substrates	Glucose (Plasma)	X	X	--	X
	Creatinine	X	X	--	X
	Bilirubin, Total	X	X	--	X
	Bilirubin, Direct	X	X	--	X
	Protein, Total	X	--	--	X
	C-Reactive Protein (Quant)	X	X	--	X
	Cholesterol, total	X	--	--	X
Electrolytes	Sodium	X	X	--	X
	Potassium	X	X	--	X
	Calcium	X	X	--	X
Urinalysis (Stix) [2]	Urine Nitrite (qual)	X	--	--	X
	Urine Protein (qual)	X	--	--	X
	Urine Glucose (qual)	X	--	--	X
	Urine Ketone (qual)	X	--	--	X
	Urobilinogen (qual)	X	--	--	X
	Urine Bilirubin (qual)	X	--	--	X
	Urine RBC/Erythrocytes (qual)	X	--	--	X
	Urine WBC/Leucocytes (qual)	X	--	--	X
	Urine pH	X	--	--	X
Urine sediment [2]	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)				

1 A, B, C and D are different sets of laboratory values. The Flow Chart details at which time point which set is to be investigated.
2 Microscopic examination if erythrocytes, leukocytes, nitrite or protein are abnormal in urine

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for pregnancy tests and drug screening, it is planned to perform these tests during screening only. Pregnancy testing in women will be performed at screening, prior to each administration of the drug cocktail, prior to the first administration of BI 730357, and as part of the end of trial examination. Drug screening will be performed at screening and upon admission on the eve of Day 1 of Visit 2 and Visit 3.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/MDMA/XTC Opiates Phencyclidine Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative) Interferon-γ release assay to tuberculosis (qualitative), e.g. QuantiFERON®-TB Gold Test
Pregnancy test (urine)	Beta human chorionic gonadotropin (beta-HCG)

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g., AlcoTrue® M, [redacted]) will be performed upon admission on the eve of Day 1 of Visit 2 and Visit 3, and may be repeated at any time during the study at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at [redacted] with the exception of drug screening and pregnancy tests. These tests will be performed at the trial site using M-10/14-PDT Surestep Multiline test and HCG-K20 test, respectively, or comparable test systems.

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

5.2.4 Electrocardiogram

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

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

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

All ECGs will be stored electronically on the Muse CV Cardiology System ([redacted]). Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists).

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

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

[redacted]

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

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

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

5.2.6.1.2 Serious adverse event

A SAE is defined as any AE which fulfils at least one of the following criteria:

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

5.2.6.1.3 AEs considered ‘Always Serious’

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

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

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

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:

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

  These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure that these parameters are analyzed, 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.
- Severe infections (grading according to Rheumatology Common Toxicity Criteria (RCTC) developed by OMERACT [R13-3515])
- Opportunistic and mycobacterium tuberculosis infections
  These include pneumocystis jirovecii, BK virus disease including polyomavirus-associated nephropathy, cytomegalovirus, posttransplant lymphoproliferative disorder (Epstein-Barr virus), progressive multifocal leukoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis (zygomycosis, rhizopus, mucor, lichtheimia), scedosporium/pseudallescheria boydii, fusarium), legionellosis, listeria monocytogenes (invasive only), tuberculosis, nocardiosis, non-tuberculous mycobacterium, salmonellosis (invasive only), hepatitis B virus reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only), paracoccidioides, penicillium marneffei, sporothrix schenckii, cryptosporidium species (chronic only), microsporidiosis, leishmaniasis (visceral only), trypanosoma cruzi Infection (Chagas' disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), hepatitis C virus progression.

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate:	Sufficient discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

5.2.6.1.6 Causal relationship of AEs

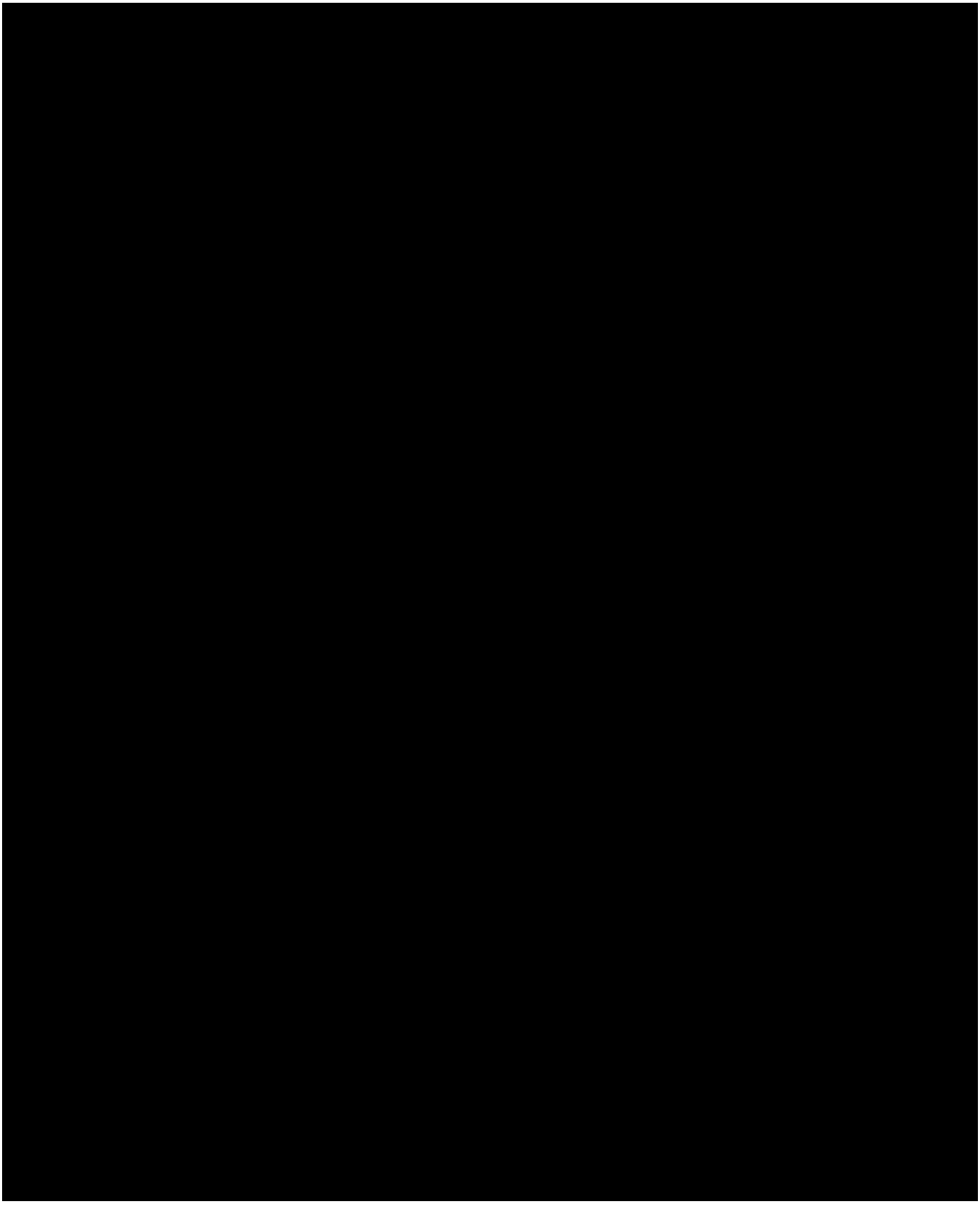
Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

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

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

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



5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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

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

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

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

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

5.2.6.2.2 AE reporting to the sponsor and timelines

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

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

5.2.6.2.3 Information required

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

5.2.6.2.4 Pregnancy

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

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

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

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

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

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

General aspects for all analytes

Blood samples for PK analyses will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle from an antecubital or forearm vein.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, planned sampling time, and the analyte (e.g., 'BI 730357' or 'CYP cocktail').

After completion of the trial, the plasma samples, the left-over, and/or back-up aliquot may be used for further methodological investigations (e.g., for stability testing or assessment of further metabolites (including, if applicable, re-analysis of parent compound). 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 trial samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR is archived.

The results of any further investigations are not planned to be part of the CTR, but can be included into the CTR if necessary.

BI 730357 and metabolite CD6975

For quantification of plasma concentrations of BI 730357 and its metabolite CD 6975, 2.7 mL of blood will be taken into K_2-EDTA (dipotassium ethylenediaminetetra-acetic acid as anticoagulant) blood-drawing tubes at the times indicated in the Flow Chart.

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 g to 4000 g and at 4 to 8 °C. From each sample, 2 plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 90 min, with interim storage of blood samples and aliquots at room temperature. Due to sensitivity of the metabolite to direct sunlight, blood samples and aliquots should not be exposed to direct sunlight. The time each aliquot was placed in the freezer will be documented.

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

Cocktail probe drugs

For quantification of plasma concentrations of caffeine, warfarin, omeprazole, and midazolam (compounds of the CYP probe cocktail) and their relevant metabolites, 7.5 mL of blood will be taken into separate K_2-EDTA blood-drawing tubes at the times indicated in the Flow Chart.

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at about 2000 g to 4000 g and 4 to 8 °C. From each sample, 4 plasma aliquots will be obtained (two primary aliquots, two back-up aliquots) and stored in polypropylene tubes. For the analysis of CYP probes (caffeine, warfarin, omeprazole, and midazolam, and their relevant metabolites) in plasma, the primary aliquots should contain at least 1.0 mL and 0.5 mL of plasma. The back-up aliquots should contain at least 0.5 mL of plasma.The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 60 min, with interim storage of blood samples in ice water or on ice The time each aliquot was placed in the freezer will be documented.

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

[redacted]

5.4 ASSESSMENT OF BIOMARKER(S)

Not applicable.

5.5 BIOBANKING

Not applicable.

[redacted]

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Sections 2.1.2, 2.1.3, 2.2.2.1, and 5.3 are generally used assessments of drug exposure.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 of Visit 2 and Days -14, -8, -1, 1, and 3 of Visit 3 are to be performed and completed within a 2 hour-period prior to the next standardized breakfast or standardized breakfast planned at the same time, if not indicated otherwise in the Flow Chart.

For ambulatory administration of BI 730357 prior to Day -1 of Visit 3 and after Day 5 of Visit 3, a time window of ± 70 minutes will be allowed.

Following cocktail administration in Visits 2 and 3, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min on Day 1, ± 45 minutes from 24 hours onwards, and ± 70 minutes from 119 hours onwards.

If scheduled in the Flow Chart at the same time as a meal, 12-lead ECG recordings, vital signs, and blood sampling have to be done first. Furthermore, if several measurements including venepuncture are scheduled for the same time, venepuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

The acceptable deviation from the scheduled time for all meals on Day 2 in Period 1 is ± 1 hour, to allow that subjects may have their meal together.

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

For cocktail PK blood sampling on Days 6-7 of Visits 2 and 3, a time window of ± 60 minutes will be allowed.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

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

[redacted]

6.2.2 Treatment periods

All subjects will undergo the following treatments (for details refer to Section 4.1):

- 100 mg caffeine, 10 mg warfarin, 20 mg omeprazole, and 2 mg midazolam together as cocktail and single oral dose on Day 1 of Visits 2 and 3
- 300 mg BI 730357 *b.i.d.* as multiple oral doses over 20 days from Day -14 until Day 6 of Visit 3

On the evening of Day -1 of Visits 2 and 3, the study participants will be admitted to the trial site and kept under close medical surveillance there until the morning of Day 3 of these visits, respectively, i.e., for at least 48 hours following administration of the cocktail containing the CYP probe drugs. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. Days on which the subjects are hospitalized are given in the Flow Chart. On all other study days, subjects will be treated in an ambulatory fashion.

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

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. For details on times of all other trial procedures, refer to the Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, assessment of SIB, and physical examination during the follow-up period, see Sections 5.2.1 to 5.2.6.
Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoTrial Visit.

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The primary objective of this trial is to investigate whether there is a drug-drug interaction between BI 730357 (as the perpetrator) and any of the drugs of the CYP probe cocktail (caffeine, S-warfarin, omeprazole, and midazolam; described in Section 1.2.2). Hence, the PK of the components of the CYP probe cocktail given as single doses without BI 730357 (Reference R) and given as single doses at steady state administration of BI 730357 (Test T) is analysed on the basis of the primary PK endpoints, as listed in Section 2.1.2. The trial is designed to allow intra-subject comparisons, and will be evaluated statistically by use of a linear model for logarithmically transformed PK endpoints.

[redacted]

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

7.2 NULL AND ALTERNATIVE HYPOTHESES

The PK of the probe drugs given alone and given at steady state administration of BI 730357 will be estimated by the ratios of the geometric means (test/reference), and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

7.3 PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were entered and treated with at least one dose of study drug. The treated set will be used for safety analyses.
- PK parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection ‘Pharmacokinetics’). Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.

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

Pharmacokinetics

The PK parameters listed in Section 2.1 for the probe drugs will be calculated by means of non-compartmental analysis. Noncompartmental PK parameters will be calculated based on actual sampling times using a validated PK software (Phoenix® WinNonlin® 6.3). Descriptive statistics will be used to evaluate plasma concentration data and PK parameters. The derivation of PK parameters is described in BI internal SOP (001-MCS-36-472). Further details on analysis will be described in the TSAP.

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 deviation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

Relevant protocol deviations may be

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

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

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

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

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

7.3.1 Primary endpoint analyses

Primary analyses

The primary endpoints (refer to Section 2.1.2) 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).

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

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

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

μ = the overall mean,

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

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

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

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

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

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

[redacted]

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

7.3.2 Secondary endpoint analyses

Not applicable.

[redacted]

7.3.4 Safety analyses

Safety will be analysed based on the assessments described in Section 2.2.2.2. All treated subjects (TS, refer to Section 7.3) will be included in the safety analysis. Safety analyses will be descriptive in nature and based on BI standards. No hypothesis testing is planned.

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

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

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

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

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity, and causal relationship of AEs will be tabulated by treatment, system organ class, and preferred term. SAEs, AESIs (see Section 5.2.6.1.4), and other significant AEs (according to ICH E3) will be listed separately.

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

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

Relevant ECG findings will be reported as AEs.

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

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

7.5.2 Pharmacokinetics

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

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

7.6 RANDOMISATION

In this trial, subjects receive all treatments in the same order, thus no randomisation for the treatment assignment is performed (see also Section 4.1.3).

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 16 subjects in the trial, account for up to 4 dropouts. The planned sample size is not based on a power calculation, but is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (test/reference) can be expected with 95% probability. Precision is defined as the ratio of upper CI limit to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

The observed intra-individual coefficient of variation (gCV) for the probe drugs ranged between 10% to over 30% in previous trials. Also, they appeared to depend on which CYP drug was evaluated. Therefore the following Table 7.7: 1 provides an overview of the two-sided 90% confidence interval of the gMean ratio (T/R) and precision (upper confidence limit/ lower confidence limit) that are expected with 95% probability, based on various assumptions around the gCVs and a sample size of N=12 evaluable subjects.

Table 7.7: 1 Expected precision and two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a two-period fixed sequence design trial (N=12)

gCV	Precision	90% CI for respective gMean %ratio (T/R)			
		20%	50%	80%	200%
10%	1.10	(18.14, 22.06)	(45.34, 55.14)	(72.55, 88.22)	(181.36, 220.55)
20%	1.21	(16.47, 24.29)	(41.18, 60.72)	(65.88, 97.15)	(164.70, 242.86)
30%	1.33	(15.00, 26.67)	(37.49, 66.68)	(59.99, 106.68)	(149.98, 266.71)

Thus, based on a sample size of N=12 evaluable subjects and assuming a gCV of 30% for the PK endpoint of the probe drug, the precision of the 90% CI would be 1.33. If the gMean ratio would be 20%, then the 90% CI is expected to range approximately from 15% to 27%.

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

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

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

The calculation was performed as described by Julious [R11-5230].

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

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

Standard medical care (prophylactic, diagnostic, and therapeutic procedures) remains the responsibility of the subject's treating physician.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

Within 1 year after trial termination the Sponsor will submit a summary of the CTR covering all relevant results of the trial to the Competent Authority and to the Independent Ethics Committee.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. As a general rule, no trial results should be published prior to archiving of the CTR.

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

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

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

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

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

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

For subjects enrolled during the COVID-19 pandemic: In addition to the study specific informed consent, separate written consent will be obtained for testing on SARS-CoV-2 infection.

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

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

ClinBase™
In the Human Pharmacology Centre (HPC) – Boehringer Ingelheim's Phase I unit – the validated ClinBase™ system is used for processing information and controlling data collected in clinical studies. In addition to its function as a procedure control system, ClinBase™ serves as data base. Instead of being entered into CRFs, selected data are directly entered into the system.

8.3.1 Source documents

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

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

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

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

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

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

Data directly entered into ClinBase™ (that is, without prior written or electronic record) are considered to be source data. The place where data are entered first will be defined in a trial specific Source Data Agreement. The data in ClinBase™ are available for inspection at any time.

8.3.2 Direct access to source data and documents

The investigator /institution will allow site trial-related monitoring, audits, IRB/IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the Clinical Research Associate, auditor and

regulatory inspector (e.g., FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site:
The trial site(s) must retain the source and essential documents (including ISF) according to the local requirements 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 AND SUBJECT PRIVACY

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

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

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

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

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

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

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

8.6 TRIAL MILESTONES

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

The **end of the trial** is defined as the 'date of the last visit of the last subject in whole trial' ('Last Subject Completed').

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

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

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

The ethics committee/competent authority in each participating EU member state will be notified about the trial milestones according to the laws of each member state.

A final report of the clinical trial data will be written only after all subjects have completed the trial in all countries (EU or non-EU), so that all data can be incorporated and considered in the report.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at the Human Pharmacology Centre (HPC) of BI Pharma GmbH & Co. KG, Biberach, Germany, under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g., their curricula vitae) will be filed in the ISF.

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

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

The trial medication will be provided by the [redacted] (BI 730357) or will be obtained by the clinical trial site from a public pharmacy (caffeine, midazolam, omeprazole, and warfarin).

Safety laboratory tests will be performed by the local laboratory of the trial site [redacted]).

The analyses of plasma concentrations of caffeine, midazolam, omeprazole, and warfarin and their metabolites as well as of BI 730357 will be performed under the responsibility of the [redacted] at suitable contract research organisations.

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 organization appointed by BI according to BI SOPs.

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

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10. APPENDICES

10.1 COLUMBA-SUICIDE SEVERITY RATING SCALE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

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

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

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

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

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

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

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

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐
If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."*
Have you been thinking about how you might do this?
Yes ☐ No ☐
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe

Most Severe Ideation: ____ _____
Type # (1-5) ***Description of Ideation***

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

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SUICIDAL BEHAVIOR *(Check all that apply; so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts ____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted ____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted ____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage, *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* ____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* ____

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11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		12 November 2020
EudraCT number		2020-002506-51
BI Trial number		1407-0039
BI Investigational Medicinal Product		BI 730357
Title of protocol		The effect of multiple doses of BI 730357 on the single dose pharmacokinetics of caffeine, warfarin, omeprazole and midazolam administered orally as a cocktail in healthy subjects (an open-label, two-period fixed sequence design trial)
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		3.3.4.1
Description of change		Clarification in the first sentence that an individual subject must be withdrawn from trial treatment by the investigator if any of the following discontinuation criteria apply. [redacted]
Rationale for change		Objections of the competent authority and ethics committee regarding the discontinuation criteria

APPROVAL / SIGNATURE PAGE

Document Number: c31764080 **Technical Version Number:2.0**

Document Name: clinical-trial-protocol-version-02

Title: The effect of multiple doses of BI 730357 on the single dose pharmacokinetics of caffeine, warfarin, omeprazole and midazolam administered orally as a cocktail in healthy subjects (an open-label, two-period fixed sequence design trial)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	13 Nov 2020 12:55 CET
Author-Trial Statistician		13 Nov 2020 13:06 CET
Approval [redacted] Medicine		13 Nov 2020 13:21 CET
Author-Trial Clinical Pharmacokineticist		13 Nov 2020 14:50 CET
Verification-Paper Signature Completion		13 Nov 2020 18:38 CET
Approval-Team Member Medicine		16 Nov 2020 13:37 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed