Clinical Trial Protocol

	Document Number:	**c32357152-03**
EudraCT No. **EU Trial No.**	2020-003097-46	
BI Trial No.	1407-0038	
BI Investigational Medicinal Product	BI 730357	
Title	The effect of BI 730357 on the pharmacokinetics of rosuvastatin, digoxin, metformin and furosemide given as a cocktail – an open-label, non-randomised, 2-period fixed-sequence trial in healthy subjects	
Lay Title	A study in healthy people to test whether BI 730357 affects how 4 other medicines (rosuvastatin, digoxin, metformin, and furosemide) are taken up in the body	
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 2))	
Version and Date	Version: 3.0	Date: 19 October 2020

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	30 July 2020
Revision date	19 October 2020
BI trial number	1407-0038
Title of trial	The effect of BI 730357 on the pharmacokinetics of rosuvastatin, digoxin, metformin and furosemide given as a cocktail – an open-label, non-randomised, 2-period fixed-sequence trial in healthy subjects
Principal Investigator	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	Evaluation of in-vivo effects of BI 730357 on drug transporter probe substrates
Trial objective	To assess the effect of multiple oral doses of BI 730357 on the pharmacokinetics of rosuvastatin, digoxin, metformin and furosemide given as a cocktail
Trial design	Non-randomised, open-label, 2-period fixed-sequence design
Trial endpoints:	Primary endpoints: $AUC_{0-\infty}$ and C_{max} of rosuvastatin, digoxin, metformin and furosemide Secondary endpoints: AUC_{0-tz} of rosuvastatin, digoxin, metformin and furosemide
Number of subjects **total entered** **each treatment**	 15 15
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 **Dose** **mode of admin.**	CRESTOR® 10 mg film-coated tablets (**rosuvastatin**) 1 x 1 tablet (10 mg rosuvastatin) Oral with 280 mL of water after a standardized breakfast
Trial product 2 **Dose** **mode of admin.**	Lenoxin® 0.25 mg tablets (**digoxin**) 1 x 1 tablet (0.25 mg digoxin) Oral with 280 mL of water after a standardized breakfast

Trial product 3	MetfoLiquid GeriaSan®, 1000 mg / 5 mL oral solution (**metformin**)
Dose	1 x 0.05 mL oral solution (10 mg metformin)
mode of admin.	Oral with 280 mL of water after a standardized breakfast
Trial product 4	Lasix® liquidum 10 mg/mL oral solution (**furosemide**)
Dose	1 x 0.1 mL oral solution (1 mg furosemide)
mode of admin.	Oral with 280 mL of water after a standardized breakfast
Trial product 5	BI 730357, 100 mg tablets
Dose	2 x 3 tablets daily (= 600 mg BI 730357 per day) during treatment Test only
mode of admin.	Oral with 240 mL of water after a standardized meal
Duration of treatment	Rosuvastatin, digoxin, metformin and furosemide are given always together as a cocktail (the cocktail). The cocktail will be given single dose in both trial periods. Treatment Reference: the cocktail Treatment Test: 3 tablets BI 730357 bid on study days -7 until study day 6 (total of 13 dosing days); on study day 1 the cocktail will be administered 1 hour after the morning dose of BI 730357 [redacted]
Statistical methods	The effect of BI 730357 on the pharmacokinetics of each of the cocktail components rosuvastatin, digoxin, metformin and furosemide will be estimated based on the ratio (test to reference) of the geometric means (gMeans) of the primary and secondary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range was not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for ‘subject’ and ‘treatment’. CIs will be calculated based on the residual error from the ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART – TREATMENT REFERENCE

Period	Visit	Day	Planned time (relative to cocktail administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory [7]	PK blood, cocktail components	PK urine, cocktail components [6, 8]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [5]
SCR	1	-21 to -2			Screening (SCR)[1]	A			x	x	x
1	2	-1	-13:00	20:00	Admission to trial site	x[4]					x
		1	-2:00	07:00			x[2]	x[2]	x[2]	x[2]	x[2]
			-1:30	07.30	Standardized breakfast						
			0:00	09:00	**Cocktail dosing**			▲			x
			0:20	09:20			x	|			
			0:40	09:40			x	|			
			1:00	10:00			x	|	x	x	x
			1:30	10:30			x	|			
			2:00	11:00	240 mL fluid intake		x	|	x	x	x
			2:30	11:30			x	|			
			3:00	12:00			x	|			
			4:00	13:00	240 mL fluid intake, thereafter lunch[3]		x	┼	x	x	x
			5:00	14:00			x	|			
			6:00	15:00			x	|			
			8:00	17:00	Extended snack[3] (voluntary)		x	┼			x
			10:00	19:00			x	|			
			10:30	19:30	Standardized dinner			|			
			12:00	21:00			x	┼			x
		2	24:00	09:00	Breakfast[3]	B	x	┼	x	x	x
			28:00	13:00	Lunch			|			x
			32:00	17:00	Snack (voluntary)			|			
			34:30	19:30	Dinner			|			
			36:00	21:00			x	┼			x
		3	48:00	09:00	Discharge, breakfast (voluntary)[3]		x	▼			x
		4	71:00	08:00	Ambulatory visit		x				x
		5	95:00	08:00	Ambulatory visit		x				x
		7	143:00	08:00	Ambulatory visit		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 (including rhythm stripe over 15 min), safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), pregnancy test in females, relevant medical history, concomitant therapy and review of inclusion/exclusion criteria. Pharmacogenetic samples will be collected if needed.
2. The time is approximate; the procedure is to be performed and completed within 3 h prior to study drug administration.
3. If several actions are indicated at the same time point, the intake of meals will be the last action.
4. Only urine drug screening, alcohol breath test and pregnancy test in females.
5. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.
6. A blank urine sample (x) is to be obtained prior to administration of trial medication. Other urine samples are to be collected over the stated post-dose intervals (◄—|—|—►) 0-4, 4-8, 8-12, 12-24, 24-36 and 36-48 h.
7. Letters A and B define different sets of safety laboratory examinations (for details refer to Section 5.2.3).

[redacted]

FLOW CHART – TREATMENT TEST

Period	Visit	Day	Planned time (relative to cocktail administration) [h:min]	Approx. clock time of actual day [h:min]	Event and comment	Safety laboratory [9]	PK blood, cocktail components	PK blood, BI 730357	PK urine, cocktail components [7, 10]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
2	3	-7	-170:30	06:30	Ambulatory visit, standardized breakfast	x[5]				x	x	
			-170:00	07:00	**Dosing BI 730357**	B						x
			-158:30	18:30	Ambulatory visit, standardized dinner							
			-158:00	19:00	**Dosing BI 730357**							x
		-6	-146:30	06:30	Ambulatory visit, standardized breakfast							
			-146:00	07:00	**Dosing BI 730357**							x
			-134:30	18:30	Ambulatory visit, standardized dinner							
			-134:00	19:00	**Dosing BI 730357**							x
		-5	-122:30	06:30	Ambulatory visit, standardized breakfast							
			-122:00	07:00	**Dosing BI 730357**							x
			-110:30	18:30	Ambulatory visit, standardized dinner							
			-110:00	19:00	**Dosing BI 730357**							x
		-4	-98:30	06:30	Ambulatory visit, standardized breakfast							
			-98:00	07:00	**Dosing BI 730357**							x
			-86:30	18:30	Ambulatory visit, standardized dinner							
			-86:00	19:00	**Dosing BI 730357**							x
		-3	-74:30	06:30	Ambulatory visit, standardized breakfast					x	x	
			-74:00	07:00	**Dosing BI 730357**	B						x
			-62:30	18:30	Ambulatory visit, standardized dinner							
			-62:00	19:00	**Dosing BI 730357**							x
		-2	-50:30	06:30	Ambulatory visit, standardized breakfast							
			-50:00	07:00	**Dosing BI 730357**							x
			-38:30	18:30	Ambulatory visit, standardized dinner							
			-38:00	19:00	**Dosing BI 730357**							x
		-1	-26:30	06:30	Ambulatory visit, standardized breakfast							
			-26:00	07:00	**Dosing BI 730357**							x
			-14:00	19:00	Admission to trial site	x[5]						x
			-13:30	19:30	Standardized dinner							
			-13:00	20:00	**Dosing BI 730357**			x[8]				x
		1	-2:00	07:00			x[2]		x[2]	x[2]	x[2]	x[2]
			-1:30	07:30	Standardized breakfast							
			-1:00	08.00	**Dosing BI 730357**			x[8]				x
			0:00	09:00	**Cocktail dosing**				▲			x
			0:20	09:20			x					
			0:40	09:40			x					
			1:00	10:00			x			x	x	x
			1:30	10:30			x					
			2:00	11:00	240 mL fluid intake		x			x	x	x
			2:30	11:30			x					
			3:00	12:00			x					
			4:00	13:00	240 mL fluid intake, thereafter lunch[3]		x			x	x	x
			5:00	14:00			x					
			6:00	15:00			x					
			8:00	17:00	Extended snack[3] (voluntary)		x			x	x	x
			10:00	19:00			x					
			10:30	19:30	Standardized dinner							
			11:00	20:00	**Dosing BI 730357**			x[8]				x
			12:00	21:00			x					x

FLOW CHART – Treatment Test, continued

Period	Visit	Day	Planned time (relative to cocktail administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory [9]	PK blood, cocktail components	PK blood, BI 730357	PK urine, cocktail components [7, 10]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
2	3	2	22:30	07:30	Standardized breakfast				┼			
			23:00	08:00	**Dosing BI 730357**			x[8]				x
			24:00	09:00		B	x		┼	x	x	x
			28:00	13:00	Lunch							x
			32:00	17:00	Extended snack[3] (voluntary)							
			34:30	19:30	Standardized dinner							
			35:00	20:00	**Dosing BI 730357**							x
			36:00	21:00			x		┼			x
		3	46:30	07:30	Standardized breakfast							
			47:00	08:00	**Dosing BI 730357**							x
			48:00	09:00	Discharge		x		▼			x
			58:00	19:00	Ambulatory visit, standardized dinner							
			58:30	19:30	**Dosing BI 730357**							x
		4	70:00	07:00	Ambulatory visit, standardized breakfast							
			70:30	07:30	**Dosing BI 730357**							x
			71:00	08:00			x					
			82:00	19:00	Ambulatory visit, standardized dinner							
			82:30	19:30	**Dosing BI 730357**							x
		5	94:00	07:00	Ambulatory visit, standardized breakfast							
			94:30	07:30	**Dosing BI 730357**							x
			95:00	08:00		B	x				x	
			106:00	19:00	Ambulatory visit, standardized dinner							
			106:30	19:30	**Dosing BI 730357**							x
		6	118:00	07:00	Ambulatory visit, standardized breakfast							
			118:30	07:30	**Dosing BI 730357**							x
			119:00	08:00			x					
			130:00	19:00	Ambulatory visit, standardized dinner							
			130:30	19:30	**Dosing BI 730357**							x
		8	167:00	08:00	Ambulatory visit		x					x
FU	4	14-22			End of trial (EoTrial) examination[4]	C				x	x	x

1. [For footnote 1 see Flow Chart of Treatment Reference]
2. The time is approximate; the procedure is to be performed and completed within 3 h prior to first drug administration.
3. If several actions are indicated at the same time point, the intake of meals will be the last action.
4. End of trial examination includes physical examination, vital signs, ECG, safety laboratory, pregnancy test in females, recording of AEs and concomitant therapies.
5. Only urine drug screening, alcohol breath test and pregnancy test in females
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.
7. A blank urine sample (x) is to be obtained prior to administration of trial medication. Other urine samples are to be collected over the stated post-dose intervals (◄—|—|—►) 0-4, 4-8, 8-12, 12-24, 24-36 and 36-48 h.
8. To be taken within 15 min prior to dosing
9. Letters A, B, and C define different sets of safety laboratory examinations (for details refer to Section 5.2.3).

[redacted]

TABLE OF CONTENTS

ABBREVIATIONS

ABC	ATP-binding cassette
AE	Adverse event
AESI	Adverse events of special interest
[redacted]	
ANOVA	Analysis of variance
AUC	Area under the concentration-time curve of the analyte in plasma
$AUC_{0-\infty}$	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
[redacted]	
BA	Bioavailability
BCRP	Breast cancer resistance protein
BI	Boehringer Ingelheim
BID	Bis in die
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
BU1	back-up sample
BU1 – BI	back-up may be used for BI 730357 analytics
[redacted]	
CA	Competent authority
CI	Confidence interval
[redacted]	
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state
CML	Clinical Monitor Local
CRF	Case Report Form

CRO	Clinical Research Organization
[redacted]	
CT	Concomitant treatment
CTP	Clinical trial protocol
CTR	Clinical trial report
CYP	Cytochrome P450
DDI	Drug-drug interaction
DNA	Desoxyribonucleic acid
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EoTrial	End of trial
F	Absolute bioavailability factor
FDA	U.S. Food and Drug Administration
[redacted]	
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
gMean	Geometric mean
HMG-CoA	3-Hydroxy-3-methylglutaryl-coenzyme A
HR	Heart rate
IEC	Independent Ethics Committee
iPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
ITC	International Transporter Consortium
Ki	Inhibition constant
K3-EDTA	Tripotassium ethylenediaminetetraacetic acid
λz	Terminal rate constant of the analyte in plasma
LC-MS/MS	Liquid chromatography tandem mass spectrometry
MATE	Multidrug and toxin extrusion protein
MATE1	Multidrug and toxin extrusion protein 1
MATE2-K	Multidrug and toxin extrusion protein 2-K
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities

[redacted]

NOA	Not analysed
NOR	No valid result
NOS	No sample available
OAT1	Organic anion transporter 1
OAT3	Organic anion transporter 3
OATP	Organic anion transporting polypeptide
OATP1B1	Organic anion transporting polypeptide 1B1
OATP1B3	Organic anion transporting polypeptide 1B3
OCT	Organic cation transporter
OCT2	Organic cation transporter 2
PD	Pharmacodynamic(s)
PE	Polyethylene
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PK D	Primary for digoxin
PK F	Primary for furosemide
PK M	Primary for metformin
PK R	Primary for rosuvastatin
PP	Polypropylene
PR	Pulse rate
q.d.	Quaque die, once daily
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	Heart frequency-corrected QT interval
R	Reference treatment
REP	Residual effect period
RS	Randomised set
SAE	Serious adverse event
SCR	Screening
SD	Single dose
SLC	Solute Carrier
SLC22A2	Gene encoding OCT2
SLC22A6	Gene encoding OAT1
SLC22A8	Gene encoding OAT3

SLC47A1	Gene encoding MATE1
SLC47A2	Gene encoding MATE2-K
SLCO1B1	Gene encoding OATP1B1
SLCO1B3	Gene encoding OATP1B3
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
Ss	(at) steady state
T	Test treatment
[redacted]	
T2DM	Type 2 diabetes mellitus
T_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set
TSAP	Trial statistical analysis plan
Tz	Time of last measurable concentration of the analyte in plasma
ULN	Upper limit of normal
[redacted]	
XTC	Ecstasy

1. INTRODUCTION

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

The trial will be performed to assess the influence of BI 730357 on the pharmacokinetics of rosuvastatin, digoxin, metformin and furosemide which are model substrates of clinically relevant drug transporters. The in-vivo effect of BI 730357 on these compounds should be used to predict potential transporter-based drug-drug interactions.

1.1 MEDICAL BACKGROUND

1.1.1 Retinoid acid-related orphan receptor γt (RORγt)

Retinoic acid-related orphan receptor γt (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. Upon cell activation, in response to multiple activation signals including cytokines and T cell receptor engagement, RORγt regulates the transcription of interleukin (IL)-17A, IL-17F, and IL-22 genes, and of the IL-23 receptor gene. Emerging clinical science indicates a pivotal role for the Th17 axis in the pathogenesis of psoriasis, and other immunologically-mediated diseases. By blocking RORγt-mediated transcription of critical pro-inflammatory cytokines, and IL-23R, and consequently their downstream signalling, RORγt antagonism could prove efficacious in the treatment of Th17-mediated diseases [c09228382].

1.1.2 Drug transporters

Drug transporters play an important role in drug absorption, distribution, and excretion. Inhibition of drug transporters by concomitantly administered drugs may cause clinically relevant drug-drug interactions (DDI) [P14-07656], [R10-1157]. With increasing recognition and understanding of the involvement of drug transporters in clinically relevant DDIs, thorough investigation of transporter-mediated DDI has become indispensable during drug development.

Based on the recommendations of the International Transporter Consortium's (ITC) white paper [R10-1157], regulatory agencies explicitly state drug transporters that should be investigated *in vitro* for inhibition by new investigational drugs during drug development. The specific transporters explicitly referred to by both the EMA guideline [P15-06991] and the FDA draft guidance [P12-05791] are the ABC transporters, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and the SLC transporters, organic anion transporting polypeptide 1B1 (OATP1B1), OATP1B3, organic cation transporter 2 (OCT2), organic anion transporter 1 (OAT1), and OAT3.

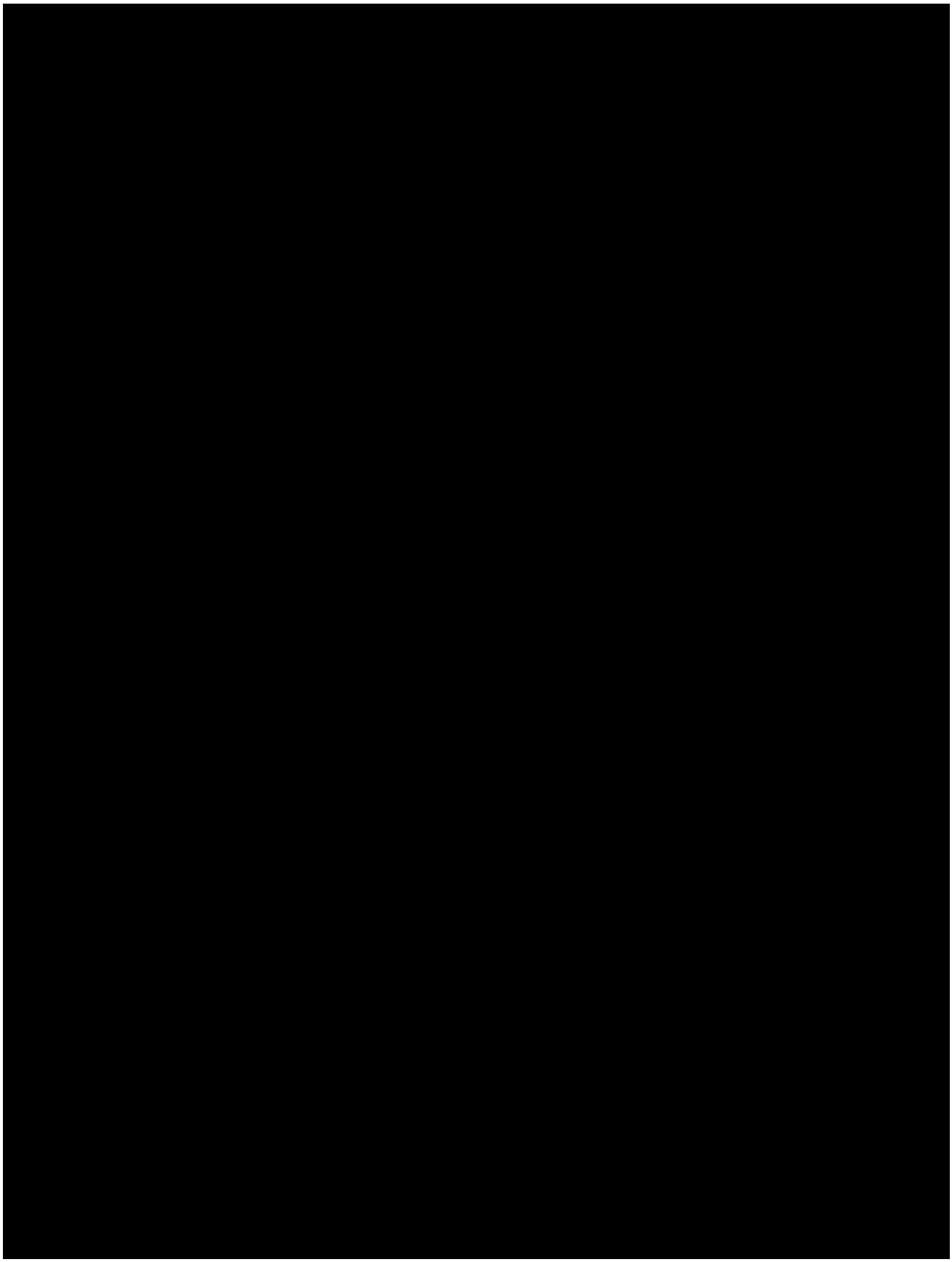
If *in vivo* inhibition of a drug transporter known to be relevant for drug disposition cannot be excluded based on *in vitro* data, an *in vivo* study is recommended by regulatory agencies. A valuable approach to investigate several separate mechanisms underlying DDIs with the

investigational product as the perpetrator in one single study is the “cocktail study”. This method, in which a mixture of well-characterized probe drugs is administered together with the new investigational product, is well established for investigation of cytochrome P450 (CYP)-mediated DDIs. Both the EMA and FDA recommend the use of cocktail studies also for the investigation of transporter-mediated DDIs [P15-06991], [P12-05791].

A cocktail of drug transporter substrates has been developed by BI during the last years. This cocktail consists of 0.25 mg digoxin (substrate of P-gp), 10 mg rosuvastatin (substrate of OATP1B1, OATP1B3 and BCRP), 10 mg metformin (substrate of OCT2, MATE1 and MATE2-K) and 1 mg furosemide (substrate of OAT1 and OAT3), thus covering all transporters of potential clinical relevance recommended by EMA and FDA (see above). In the given doses the cocktail demonstrated no mutual interactions [R20-1915]. The metabolism of these drugs is minor facilitating the investigation of transporter-mediated DDIs without enzyme inhibition potentially confounding the results.

In this trial the BI transporter cocktail will be used for the first time to investigate the transporter-based DDI potential of a development compound.

1.2 DRUG PROFILE



1.2.2 Rosuvastatin

Rosuvastatin is an HMG-CoA reductase inhibitor indicated for treatment of hypercholesterolemia and for prophylaxis of cardiovascular events. Inhibition of HMG-CoA decreases hepatic cholesterol production which, in turn, stimulates hepatocellular uptake of low-density lipoproteins [R17-2886].

After oral administration, maximal rosuvastatin plasma concentrations are reached at ~5 h. Oral bioavailability is ~20%, plasma protein binding is ~90%, and V_Z/F is ~134 L. The liver is a principal compartment of distribution, with hepatocellular uptake being mediated mainly by OATP1B1 and, to a lesser degree, by OATP1B3. Elimination is mainly via faeces and to a lesser degree, via urine (principally via renal tubular secretion), with a $t_{1/2}$ of 19 h [R17-2886], [P14-07833].

In therapy, the initial rosuvastatin dose is 5-10 mg once daily (q.d.), and during therapy, the daily dose may be increased to up to 40 mg [R17-2886].

Adverse reactions to rosuvastatin are normally mild and transient. Myalgia and myopathy with concomitant increase of creatine kinase, and, in rare cases, rhabdomyolysis have been observed during rosuvastatin therapy. Moreover, as for other HMG-CoA reductase inhibitors, a dose-dependent increase of liver transaminases may be observed [R17-2886].

For a complete listing of adverse reactions, including frequency of occurrence, please refer to the current SmPC [R19-3033].

1.2.3 Digoxin

The cardiac glycoside digoxin is a potent and specific inhibitor of the membrane-bound Na^+/K^+ ATPase. In cardiomyocytes, Na^+/K^+ ATPase inhibition increases intracellular Ca^{++} concentrations during electromechanic coupling. Digoxin has positive inotropic and bathmotropic and negative chronotropic and dromotropic cardial effects. Use of digoxin is indicated in patients with tachyarrhythmia absoluta due to atrial fibrillation or flutter, with congestive heart failure due to systolic dysfunction, or with paroxysmal atrial fibrillation or flutter [R16-2173].

Digoxin oral bioavailability is ~60-80%. Its volume of distribution is large at 510 L in healthy volunteers; plasma protein binding is ~20%. Digoxin is eliminated principally (~80%) by the kidney, with a $t_{1/2}$ of approximately 40 h [R16-2173].

In therapy, digoxin is given first as a loading regime of up to 0.75 mg digoxin/day, followed by a maintenance regime controlled by therapeutic drug monitoring.

Adverse reactions to digoxin include cardiac arrhythmia, gastrointestinal complaints and diverse symptoms of the central nervous system such as headache or psychiatric disorders. Moreover, disturbances of colour vision may occur. In rare cases, gynecomasty, myasthenia, thrombocytopenia, hypersensitivity reactions or lupus erythematodes have been observed [R16-2173]. A complete listing of adverse reactions, including frequency of occurrence, may be found in the current SmPC.

Symptoms of digoxin toxicity include cardial, gastrointestinal, and central side effects. Moreover, hyperkalemia may occur in acute overdosing. Life-threatening intoxications were observed after doses of ≥ 10 mg digoxin [R16-2173].

For a complete listing of adverse reactions please refer to the current SmPC [R20-2007].

1.2.4 Metformin

Metformin is an oral antidiabetic that reduces plasma glucose concentrations by decreasing intestinal glucose absorption and hepatic glucose production and by enhancing glucose utilization in peripheral tissues. Thus, metformin reduces basal (fasting) and postprandial plasma glucose in patients with type 2 diabetes mellitus (T2DM). However, metformin does not stimulate insulin secretion and is not causally related to hypoglycaemia in patients with T2DM or in healthy volunteers. Metformin is used in patients with T2DM if sufficient reduction of plasma glucose is not reached by diet and exercise alone [R17-3544].

After oral administration, t_{max} is reached at ~2.5 h, and oral bioavailability (of 500-850 mg) is ~50-60%. Plasma protein binding is negligible, however, metformin enters erythrocytes which probably compose a deep distribution compartment. CL_R of metformin is high

(estimated population mean of 507 ± 129 mL/min) and the principal mode of elimination, with a $t_{1/2}$ of approximately 6.5 h [R17-3544], [P11-01873].

The initial metformin dose is normally 500-850 mg up to three times daily. The dose may be increased to up to 3000 mg per day [R17-3544].

Most frequent adverse reactions to metformin are gastrointestinal complaints such as nausea, vomiting, diarrhoea, abdominal pain, or appetite loss. Moreover, metformin may cause changed taste (e.g., metallic taste), and, very rarely or with unknown frequency, respectively, skin reactions or abnormal liver function tests. For a complete listing of adverse reactions, including frequency of occurrence, please refer to the current version of the SmPC [R17-3544].

In addition, metformin may, very rarely, cause lactic acidosis. This is a life-threatening disorder caused by metformin accumulation, principally in diabetic patients with severe renal insufficiency. In case of unspecific symptoms such as muscle cramps in combination with gastrointestinal disorder or severe asthenia, lactic acidosis needs to be taken into account. Other possible symptoms are dyspnoea, abdominal disorders, hypothermia, and coma [R17-3544]. To our knowledge, lactic acidosis has not been observed in healthy volunteers, so far. High doses of up to 85 g metformin did not cause hypoglycaemia. However, lactic acidosis has been observed with this severe overdosing [R17-3544].

For a more detailed description of metformin`s profile please refer to the current SmPC [R17-3544].

1.2.5 Furosemide

Furosemide is a loop diuretic indicated for treatment of oedema (cardiac, hepatic, renal, or due to burns), arterial hypertension, oliguria or pulmonary oedema. By inhibition of the $Na^+/2Cl^-/K^+$ carrier in the distal ascending limp of Henle's loop, furosemide increases diuresis and excretion of sodium, potassium, calcium, and magnesium [R16-2538].

After administration of furosemide as an oral solution, oral bioavailability is ~80%. Maximal plasma concentrations (t_{max}) are observed at ~1 h. Plasma protein binding is 95%, and V_Z/F is 0.2 L/kg. Furosemide is eliminated principally as unchanged substance, to two thirds by the kidney (glomerular filtration and secretion) and to one third by excretion into bile [R16-2538].

In therapy, initial doses of oral furosemide are normally 40 mg, but higher doses of over 200 mg are possible in individual cases when diuresis with lower doses is not sufficient. Maintenance dose is normally 40-80 mg/day [R16-2538].

Adverse reactions include mainly electrolyte disorders including dehydration and hypovolemia, hearing disorders and allergic reactions including skin reactions.

Symptoms of overdosing are characterized by excessive loss of electrolytes which may lead to hypotension, syncope, or delirium [R16-2538].

For a complete listing of furosemide adverse reactions, including frequency of occurrence, please refer to the current SmPC [R20-2008].

1.2.6 Residual Effect Period

The Residual Effect Period (REP) of the cocktail is 10 days referring to digoxin, 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) [redacted] 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

Based on non-clinical data, [redacted] This trial aims to investigate the in-vivo effect of BI 730357 on these drug transporters by using the drug transporter model substrates rosuvastatin (OATP1, BCRP), digoxin (P-gp), metformin (MATE-1, MATE-2K) and furosemide (OAT1) which will be administered as a cocktail (see Section 1.1.2). The results of this trial will guide predictions on the DDI potential of BI 730357 with respect to the inhibition of the investigated drug transporters.

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 psoriasis 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.

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

1.4.2 Drug-related risks

[redacted]

[redacted]

1.4.2.2 Risks related to the administration of the cocktail (without transporter inhibition)

All four cocktail components are market-approved drugs. The doses used in this trial are within or below the therapeutic range (see Table 1.4.2.2: 1).

Table 1.4.2.2: 1 Doses of cocktail components used in this trial compared to their therapeutic doses and to reported doses that have been given to healthy volunteers (HV):

Drug	Dose in this trial	Therapeutic daily dose	Dose tolerated by HV
digoxin	0.25 mg SD	0.2 – 0.4 mg [R16-2173]	0.75 mg SD [R17-1846]
furosemide	1 mg SD	40 – 80 mg [R16-2538]	80 mg SD [R17-1848]
metformin	10 mg SD	up to 3000 mg [R17-1837]	1000 mg SD [U13-2366-01]
rosuvastatin	10 mg SD	10 mg – 40 mg [R17-2886]	80 mg SD [R13-4572]

While digoxin and rosuvastatin are given in therapeutic doses, subtherapeutic doses are used for furosemide and metformin. All these doses have been well tolerated by healthy subjects in the cocktail validation studies [R17-0548, R18-0240, R20-1915, R20-1930].

1.4.2.3 Risks related to a potential inhibition of drug transporters by BI 730357

[redacted]

Rosuvastatin is a substrate of OATP1B1/OATP1B3 and BCRP. Rifampicin is a known strong inhibitor of OATP transporters. After combined administration of rifampin and rosuvastatin Lai et al. and Pruesaritanont et al. describe an about 10-13-fold increase of rosuvastatin C_{max}

and a 5-fold increase of rosuvastatin AUC [R15-4771], [R17-1790]. This effect size could be confirmed by our cocktail validation trial 352.2100, in which a dose of 10 mg rosuvastatin has been given together with rifampicin and was well tolerated [c23988236-01].

[redacted] In a DDI study with itraconzole using single doses of 80 mg rosuvastatin Cooper et al report a rosuvastatin plasma exposure of AUC of 571 ng/mL*h and C_{max} of 61 ng/mL, that was well tolerated by healthy subjects [R13-4572] providing a safety margin of 13 (AUC) and 14.7 (C_{max}) compared to the exposure after 10 mg rosuvastatin seen in 352.2082. This is assessed to be sufficient to cover the potential inhibition of OATP1B1/1B3 mediated by BI 730357.

Clinical data on the effect size of a specific inhibition of BCRP are not available. Thus, the risk resulting from an increased rosuvastatin exposure following a potential combined inhibition of OATPs and BCRP by BI 730357 cannot be assessed.

Digoxin is a model substrate of P-gp. Several P-gp inhibitors have been tested with digoxin [P09-01856]. The greatest effect on digoxin exposure has been observed with valspodar which increased AUC and C_{max} of digoxin by Factor 3 and 2.5 [R07-4702].

In this trial, 0.25 mg digoxin will be given. According to the literature, single doses of 0.75 mg digoxin have been well tolerated by healthy subjects [R17-1846], [R17-1847]. Assuming dose-proportional kinetics, this would provide a safety margin of factor 3, which is assessed to be sufficient to cover the potential inhibition of P-gp mediated by BI 730357.

Metformin is a substrate of OCT2 and MATE-transporters. Cimetidine is a known strong inhibitor of these transporters. The greatest effect of cimetidine on metformin exposure has been reported by Somogyi et al. The combined administration of cimetidine and metformin increased metformin C_{max} and AUC by 73% and 46%, respectively [R99-0743].

In this trial a dose of 10 mg metformin will be given. Considering that therapeutic doses of 1000 mg metformin have been well tolerated by healthy subjects [U13-2366-01], no undue risk is expected from combined administration of metformin and BI 730357 in this study.

Furosemide is a substrate of OAT1 and OAT3. Probenecid is a known strong inhibitor of these drug transporters. Smith and Vree observed an approximately 3-fold increase of furosemide AUC after combined administration of probenecid and 40 mg [R17-1861] and 80 mg [R17-1859] furosemide. [redacted]

1.4.2.4 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 5.2.5.1.4, adverse events of special interest.

1.4.3 Safety measures

For safety measures and assessments such as screening examination, AE/CT questioning, laboratory examinations, in-house periods or ECG/vital signs measurements, 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.

1.4.4 Overall assessment

Digoxin, metformin, rosuvastatin and furosemide have been well tolerated after increase of their exposure mediated by established inhibitors [c23988236-01]. Thus, a potential increase in drug exposure of rosuvastatin, digoxin, metformin and furosemide mediated by BI 730357 administration is covered by the experience made in previous trials (Section 1.2.1.3).

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 investigate the effect of BI 730357 under steady state conditions on the pharmacokinetics of digoxin, furosemide, metformin and rosuvastatin given as a cocktail (Reference, R: cocktail alone; Test T: cocktail given under steady state conditions of BI 730357).

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined for rosuvastatin, digoxin, metformin and furosemide:

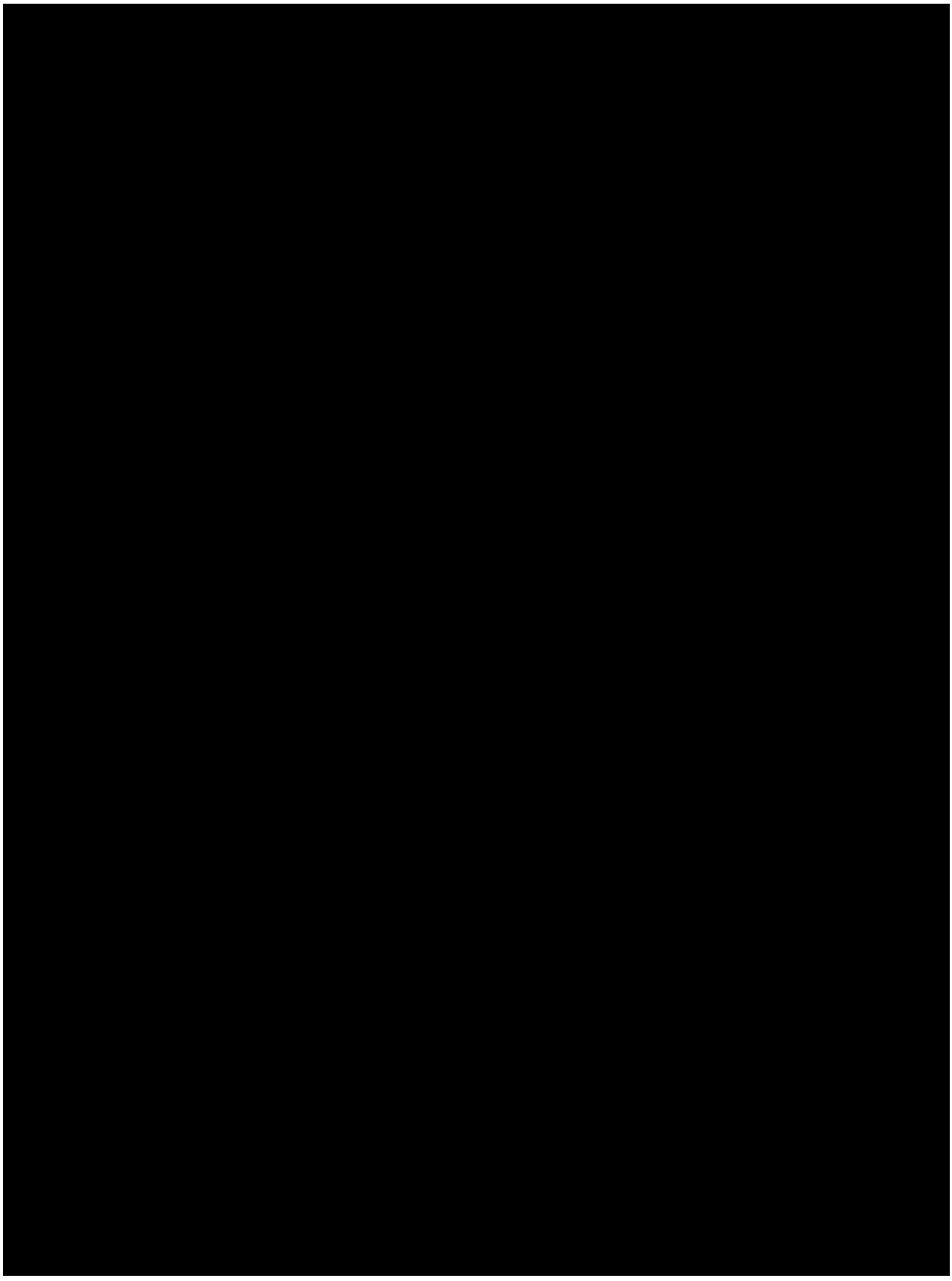
- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)
- C_{max} (maximum measured concentration of the analyte in plasma)

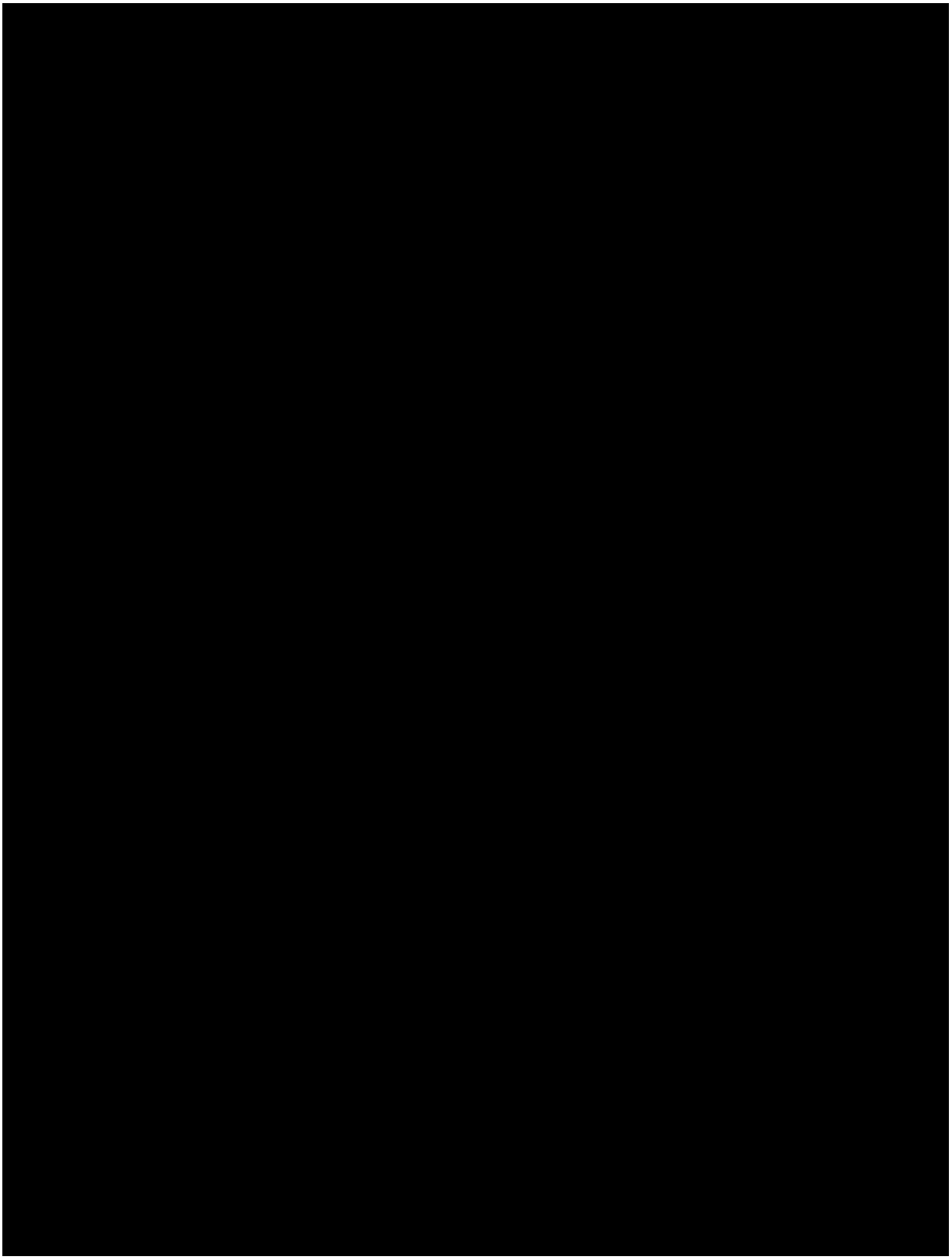
2.1.3 Secondary endpoint

The following pharmacokinetic parameter will be determined for rosuvastatin, digoxin, metformin and furosemide:

- 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)

[redacted]





2.2.2.5 Safety and tolerability

Safety and tolerability of BI 730357, rosuvastatin, digoxin, metformin and furosemide will be assessed based on:

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

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as a non-randomised, open-label, 2-period fixed-sequence trial in healthy male and female subjects in order to compare the test treatment (T) to the reference treatment (R). An overview of both treatments is given below, for details refer to Section 4.1.

Treatment Reference (R)

- The cocktail (consisting of 10 mg rosuvastatin, 0.25 mg digoxin, 10 mg metformin and 1 mg furosemide) given alone on Day 1 of period 1

Treatment Test (T)

- The cocktail given one hour after the morning administration of BI 730357 on Day 1 of period 2; pre-dosing with BI 730357 occurred on Day -7 to -1; dosing of BI 730357 will be continued until Day 6; dosing regimen of BI 730357 is 300 mg bid for 13 days

All treatments will be given after a standardised meal. Reference treatment will always be followed by the Test treatment in a fixed sequence. [redacted]

The subjects will be divided into 2 cohorts. The first cohort should contain not more than 6 subjects. Dosing of the 2nd cohort should start at least 5 days after the 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.

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

For this trial, the crossover design is preferred because of its efficiency: since each subject serves as his/her 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 different treatment time schedules, [redacted] a fixed-sequence design was selected, in which BI 730357 was administered in the second study period only. The fixed-sequence design is not expected to lead to systematic errors in the estimation of the treatment effects since non-specific time-effects are unlikely due to the short trial duration.

The open-label treatment is not expected to bias results, since the study endpoints are derived from measurement of plasma and urine concentrations of the analytes, which are provided by a bioanalytical laboratory that is blinded to treatment allocation.

[redacted]

3.3 SELECTION OF TRIAL POPULATION

It is planned that 15 healthy male and female subjects (if feasible at least 5 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 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. Male subjects, or female subjects who meet any of the following criteria from at least 30 days before the first administration of trial medication until 30 days after trial completion:
   - Use of adequate contraception, e.g. any of the following methods *plus* condom: implants, injectables, combined oral or vaginal contraceptives, intrauterine device
   - Sexually abstinent
   - 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 that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
12. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
13. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (intake of more than 20 g per day for females and 30 g per day for males)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
18. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
19. Inability to comply with the dietary regimen of the trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males or repeatedly greater than 470 ms in females) or any other relevant ECG finding at screening
21. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
23. Male subjects with WOCBP partner who are unwilling to use male contraception (condom or sexual abstinence) from time point of first administration of trial medication until 30 days after the last administration of trial medication
24. For female subjects, positive pregnancy test, pregnancy, or plans to become pregnant within 30 days after study completion

25. For female subjects, lactation period
26. During COVID-19 pandemic: laboratory test indicative of an ongoing SARS-CoV-2 infection
27. Hypokalemia, hypomagnesemia, or hypercalcemia
28. PQ interval greater than 220 ms in the ECG at screening
29. Marked conductivity disorders (e.g. sinu-atrial blocks of II° or III°) or sick sinus syndrome, thoracic aneurysm of the aorta
30. Known or suspicion of pre-excitation syndrome (WPW- or LGL syndrome)
31. Known myopathy, personal or family history of hereditary muscular disorders, or history of muscular toxicity with another statin or fibrate; Asian ancestry; hypothyroidism
32. Hereditary fructose intolerance, lactose intolerance, glucose-galactose malabsorption, sucrose-isomaltase deficiency
33. History of nephrolithiasis
34. Gout or clinically relevant elevation of uric acid
35. Clinically relevant hypoproteinemia at screening
36. TSH exceeds upper limit of norm at screening, confirmed by a repeat test
37. Creatinine clearance (according to CKD EPI formula) is lower than 80 ml/min confirmed by a repeat test
38. Subjects with any other condition that would preclude administration of digoxin, furosemide, metformin or rosuvastatin (i.e. contraindicated as per SmPC), such as hypersensitivity to active ingredient or any of the excipients or to sulphonamides, active liver disease including elevations of serum transaminases exceeding 2 times the upper limit of normal upon repeat test, hypovolaemia or dehydration, partial obstructions of urinary outflow (e.g. prostatic hypertrophy)

For study restrictions, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

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

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

and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

If it is known that a subject becomes pregnant during the trial, administration of the trial medication is to be stopped immediately, and the subject is to be removed from the trial. The subject is to be followed until she has given birth or until the end of the pregnancy. The subject's data are to be collected until the end of the trial (last visit of last subject) and reported in the CTR. For reporting of pregnancy and associated events, refer to Section 5.2.5.2.4.

3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

1. The subject wants to discontinue trial treatment, without the need to justify the decision
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as pregnancy, surgery, adverse events [AEs], or diseases)
5. The subject has an elevation of AST and/or ALT ≥3-fold ULN 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. In addition to these criteria, the investigator may discontinue subjects at any time based on his or her clinical judgment.

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

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects have drug-related and clinically relevant adverse events

of moderate or severe intensity, or if at least 1 drug-related serious adverse event is reported

2. Violation of GCP, or the CTP impairing the appropriate conduct of the trial
3. The sponsor decides to discontinue the further development of the investigational product

3.3.5 Replacement of subjects

In case more than 3 subjects do not complete the trial, the Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

BI 730357 will be provided by BI Pharma GmbH & Co. KG, Germany. Rosuvastatin, digoxin, metformin and furosemide 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

Name:	* CRESTOR® 10 mg Film-coated tablet
Substance:	Rosuvastatin (as rosuvastatin calcium)
Pharmaceutical formulation:	Film-coated tablet
Holder of marketing authorization:	[redacted]
Unit strength:	10 mg
Posology:	1 – 0 – 0 (cocktail component)
Route of administration:	Oral
Duration of use:	single dose on Day 1 of visit 2 and 3

Trial product 2

Name:	* Lenoxin® 0,25 mg tablets
Substance:	Digoxin
Pharmaceutical formulation:	Tablet
Holder or marketing authorization:	[redacted]
Unit strength:	0.25 mg
Posology:	1 – 0 – 0 (cocktail component)
Route of administration:	Oral
Duration of use:	single dose on Day 1 of visit 2 and 3

Trial product 3

Name:	* MetfoLiquid GeriaSan® 1000 mg/5 ml oral solution
Substance:	Metformin hydrochloride
Pharmaceutical formulation:	Oral solution
Holder of marketing authorization:	[redacted] Co-marketing: [redacted]
Unit strength:	1000 mg/5 mL
Posology:	0.05 mL (10 mg) – 0 – 0 (cocktail component)
Route of administration:	Oral
Duration of use:	single dose on Day 1 of visit 2 and 3

Trial product 4

Name:	* Lasix® liquidum 10 mg/ml oral solution
Substance:	Furosemide (as furosemide sodium)
Pharmaceutical formulation:	Oral solution
Holder of marketing authorization:	[redacted]
Unit strength:	10 mg/mL
Posology:	0.1 mL (1 mg) – 0 – 0 (cocktail component)
Route of administration:	Oral
Duration of use:	single dose on Day 1 of visit 2 and 3

* These trial products may be replaced by generics which will be announced via a non-substantial CTP amendment.

Trial product 5

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:	from Day -7 to Day 6 of Visit 3 (13 days in total)

4.1.2 Selection of doses in the trial

[redacted] 0.25 mg digoxin, 1 mg furosemide, 10 mg metformin hydrochloride and 10 mg rosuvastatin (see Section 1, Introduction).

[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 study subject number by drawing lots prior to first administration of trial medication in the morning of Day 1 of Visit 2.

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

4.1.4 Drug assignment and administration of doses for each subject

This trial is a non-randomised 2-period fixed-sequence study. All subjects will receive the two treatments in a fixed sequence (Reference always followed by Test). The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total daily dose
R (cocktail)	Digoxin	Tablet	0.25 mg	1 tablet as single dose	0.25 mg
	Furosemide	Oral solution	10 mg/mL	0.1 mL (1 mg) as single dose	1 mg
	Metformin	Oral solution	1000 mg/5mL	0.05 mL (10 mg) as single dose	10 mg
	Rosuvastatin	Film-coated tablet	10 mg	1 tablet as single dose	10 mg
T	BI 730357	Film-coated tablet	100 mg	3 tablets (300 mg) bid for 13 days **on Day 1 the morning dose is given 1 h prior to the cocktail**	600 mg
	Digoxin	Tablet	0.25 mg	1 tablet as single dose	0.25 mg
	Furosemide	Oral solution	10 mg/mL	0.1 mL (1 mg) as single dose	1 mg
	Metformin	Oral solution	1000 mg/5mL	0.05 mL (10 mg) as single dose	10 mg
	Rosuvastatin	Film-coated tablet	10 mg	1 tablet as single dose	10 mg

The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water (BI 730357) or 280 ml (for the cocktail) to subjects who are in 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.

Fed conditions

A standardized meal (bread roll with butter, cheese and/or sliced sausage) will be served 30 min before each BI 730357 administration. The subjects must completely consume the meal prior to drug intake. To assure comparable conditions for the cocktail administration, the standardised meal will be served also in the Reference treatment 90 min prior to the planned dosing of the cocktail (the meal is to be consumed within 30 min).

[redacted]

Thereafter, complete drug administration is assumed.

All components of the cocktail should be administered within 2 minutes.

After cocktail administration (in R and T)

Subjects will be kept under close medical surveillance until 48 h following cocktail administration. During the first 4 h after cocktail administration, they are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture), unless required for medical procedures. For restrictions with regard to diet, see Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

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

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

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

4.1.6 Packaging, labelling, and re-supply

BI 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.

Rosuvastatin, digoxin, metformin and furosemide

Rosuvastatin, digoxin, metformin and furosemide will be obtained 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 local clinical monitor (as provided in the list of contacts) is to be contacted immediately.

4.1.8 Drug accountability

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

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

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

The investigator or designee must maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each subject, and the disposal of unused products. These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational medicinal product and trial subjects. 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 all unused or partially used drug supplies have been returned by the clinical trial subject and 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 adverse events require treatment, the investigator can authorise symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all results of medical evaluations are acceptable.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

[redacted]

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects are restricted from consuming any other foods or drinks than those provided by the staff. Standardised meals will be served at the time points described in the Flow Chart. No food is allowed for at least 4 h after intake of the cocktail.

On Day 1 of both treatment periods from 1 h before (first) drug intake until lunch, fluid intake is restricted to the water administered with the drugs, and an additional 240 mL of water at 2 h and 4 h after cocktail administration (mandatory for all subjects).

In all periods total fluid intake on Day 1 is restricted to 3000 mL from lunch until 24 h post-dose. From 24 h – 48 h post-dose (in-house confinement) the total fluid intake is restricted to 4000 mL. The term “post-dose” refers to the cocktail administration in both trial periods.

Green tea, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products including St. John's wort (Hypericum perforatum) are not permitted starting 7 days before the first study drug administration until last PK sampling of the trial.

Alcoholic beverages are not permitted starting 48 h before the first study drug administration until last PK sampling of the trial.

Methylxanthine-containing drinks or foods (such as coffee, white or black tea, cola, energy drinks, and chocolate) are not allowed from 12 h before administration of trial medication until subsequent discharge from the study site.

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

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

Direct exposure to the sun or exposure to solarium radiation, treatment with ultraviolet light (e.g. PUVA), or medication with known phototoxicity potential (e.g, doxycycline) should be avoided from the first administration of BI 730357 until the EoTrial examination. The use of sunscreens is mandatory during 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 study centre under supervision of the investigating physician or a designee. The measured plasma concentrations and urinary excretion of trial medication will provide additional confirmation of compliance.

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (results 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 (including rhythm strip), laboratory tests, and physical examination.

At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and physical examination.

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 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in the Flow Chart after the subjects have fasted for at least 10 h with the exception of safety lab B which may be taken under non-fasted conditions. For retests, at the discretion of the investigator or designee, overnight fasting is not required.

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

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. Blood sampling for lymphocyte differentiation may be separated from the rest of safety lab B, should safety lab B fall on a Sunday. In these cases blood for lymphocyte differentiation will be withdrawn in an additional blood sample on Sunday evenings to ensure sufficient stability of samples until measurement the next day. This is acceptable since it is only a logistical step which ensures sample stability but does not influence the timepoint of availability of these safety data, i.e. only on the Monday either way, and has no impact on subjects' safety.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A[1]	B[1]	C[1]
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X
	White Blood Cells/Leucocytes	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	-	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	-	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs); Neut. Poly (segs), absol.; Neutrophils Bands; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/ Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.			
Lymphocyte differentiation (relative and absolute; except for ratio)	T cells (CD3+), T helper cells (CD3+CD4+), cytotoxic T cells (CD3+CD8+), B cells (CD19+), natural killer cells (CD16+CD56+CD3-), double-positive T cells (CD3+CD4+CD8+), CD4:CD8 ratio	X	X	X
Coagulation	Activated Partial Thromboplastin Time	X	-	X
	Prothrombin time - INR (International Normalization Ratio)	X	-	X
Enzymes	AST [Aspartate transaminase] /GOT	X	X	X
	ALT [Alanine transaminase] /GPT	X	X	X
	Alkaline Phosphatase	X	X	X
	Gamma-Glutamyl Transferase	X	X	X
	Creatine Kinase [CK]	X	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	-	-	-
Hormones	Thyroid Stimulating Hormone	X	-	-
Substrates	Glucose (Plasma)	X	-	-
	Creatinine	X	X	X
	GFR/ CKD-EPI[3]	X	-	-
	Bilirubin, Total	X	-	X
	Bilirubin, Direct	X	-	X
	Protein, Total	X	-	X
	C-Reactive Protein (Quant)	X	X	X
	Uric Acid	X	-	-
Electrolytes	Sodium	X	X	X
	Potassium	X	X	X
	Calcium	X	X	X
	Magnesium	X	X	X
	Chloride	X	X	X

Cont'd Table 5.2.3: 1 Routine laboratory tests

Urinalysis[2] (Stix)	Urine Nitrite (qual)	X	-	-
	Urine Protein (qual)	X	-	-
	Urine Glucose (qual)	X	-	-
	Urine Ketone (qual)	X	-	-
	Urobilinogen (qual)	X	-	-
	Urine Bilirubin (qual)	X	-	-
	Urine RBC/Erythrocytes (qual)	X	-	-
	Urine WBC/Leucocytes (qual)	X	-	-
	Urine pH	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)			
[redacted]				

1 A to be done at screening examination, B during the trial, C at EoTrial examination.
2 Microscopic examination if erythrocytes, leukocytes, or protein are abnormal in urine
3 Estimated glomerular filtration rate according to CKD-EPI formula [R12-1392]
[redacted]

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, upon admission in the evening of Day -1 of both treatment periods, 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 in the evening of Day -1 of both treatment periods.

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) [redacted]
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 in the evening of Day -1 of both treatment periods, 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 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 sec duration after subjects have rested for at least 5 min in a supine position. ECG assessment will always precede all other study procedures scheduled for the same time to avoid compromising ECG quality.

All ECGs will be stored electronically on the Muse CV Cardiology System ([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.

5.2.5 Assessment of adverse events

5.2.5.1 Definitions of adverse events

5.2.5.1.1 Adverse event

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

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

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

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

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

5.2.5.1.2 Serious adverse event

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

- Results in death
- Is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe
- Requires inpatient hospitalisation
- Requires prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect

- Is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse

5.2.5.1.3 AEs considered 'Always Serious'

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the trial medication and must be reported as described in Section 5.2.5.2, 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.

5.2.5.1.4 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 5.2.5.2.2.

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.

5.2.5.1.5 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

5.2.5.1.6 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

5.2.5.2 Adverse event collection and reporting

5.2.5.2.1 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.

5.2.5.2.2 AE reporting to the sponsor and timelines

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

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

5.2.5.2.3 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.

5.2.5.2.4 Pregnancy

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

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

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

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

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

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis (cocktail components)

For quantification of digoxin, furosemide, metformin and rosuvastatin plasma concentrations (cocktail components to be analysed from primary aliquots; [redacted] 7.5 mL of blood will be taken from an antecubital or forearm vein into K_2-EDTA anticoagulant blood drawing tubes at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for at least 15 min at approximately 2000 x g to 4000 x g and at 4 to 8 °C. Centrifugation should be started within 45 minutes after sampling. Seven plasma aliquots (4 primaries and 3 back-ups) will be obtained and stored in polypropylene tubes. The primary aliquots should contain at least 0.4 mL plasma, the back-up aliquots 0.4 ml (BU1 and BU2), and approximately 0.8 ml (BU3).

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 in ice water or on ice until centrifugation. [redacted]

For each aliquot, the time when the sample was placed in the freezer will be documented. Until transfer on dry ice, the aliquots will be stored upright at about -20°C or below at the trial site. The primary aliquots will be sent to the bioanalytical laboratory first. They will be sent in two shipments; the second shipment will be sent only after the bioanalytical laboratory has acknowledged safe arrival of the first shipment. At the bioanalytical laboratory, the primary aliquots will be stored at about -20°C or below until analysis. [redacted]

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

- “A1 - PK D” = primary for digoxin
- “A2 - PK F” = primary for furosemide
- “A3 - PK M” = primary for metformin

- "A4 - PK R" = primary for rosuvastatin

[redacted]

5.3.2.2 Blood sampling for pharmacokinetic analysis (BI 730357 trough samples)

For quantification of BI 730357 plasma concentrations 2.7 mL of blood will be taken from an antecubital of forearm vein into a separate K_2-EDTA (dipotassium ethylenediaminetetra-acetic acid as anticoagulant) blood drawing tubes at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by veni-puncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 x g to 4000 x g and at 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL of plasma.

The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 120 min with interim storage of blood samples at room temperature and without exposition to direct sunlight.

The time each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, BI 730357 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 about -20°C or below until analysis.

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'). Further information such as matrix may also be provided.

5.3.2.3 Urine sampling for pharmacokinetic analysis

A blank urine sample will be collected before administration of trial medication (see Flow Chart) and aliquots will be retained to check for analytical interference. All urine voided during the sampling intervals indicated in the Flow Chart will be collected in 2 L polyethylene (PE) containers and stored at room temperature. Subjects are told to empty their bladders at the end of each sampling interval.

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

For each sampling interval or time point seven urine aliquots of at least 2 mL will be obtained (4 primaries, 2 back-ups [redacted]

For the 4 primaries and the 2 back-ups: Until transfer on dry ice, the urine samples will be stored at about -20°C or below at the trial site. For all treatment periods, the primary aliquots will be sent to the bioanalytical laboratory first. They will be sent in two shipments; the second shipment will be sent only after the bioanalytical laboratory has acknowledged safe arrival of the first shipment. At the bioanalytical laboratory, the primary aliquots will be stored at about -20°C or below until analysis.

The back-up aliquots will only be transferred to the analytical laboratory analysing cocktail components if needed (primary aliquots are foreseen for these analyses). In any case, back-up aliquots will only be shipped from the clinical site once the bioanalyst has acknowledged safe arrival of the primary aliquots at the analytical laboratory.

[redacted]

At minimum, the sample tube labels should list the following information: BI trial number, subject number, visit number, aliquot, and planned collection interval or time point, as applicable. Further information, such as matrix, may also be provided.

The aliquot names are planned as follows:

- "A1 - PKU D" = primary for digoxin
- "A2 - PKU F" = primary for furosemide
- "A3 - PKU M" = primary for metformin
- "A4 - PKU R" = primary for rosuvastatin

[redacted]

5.3.2.4 Further investigations

After completion of the analysis of plasma and urine samples for concentrations of digoxin, furosemide, metformin, and rosuvastatin, the plasma and urine samples (including back-ups and left-over sample volumes from pre-specified analyses) may be used as follows:

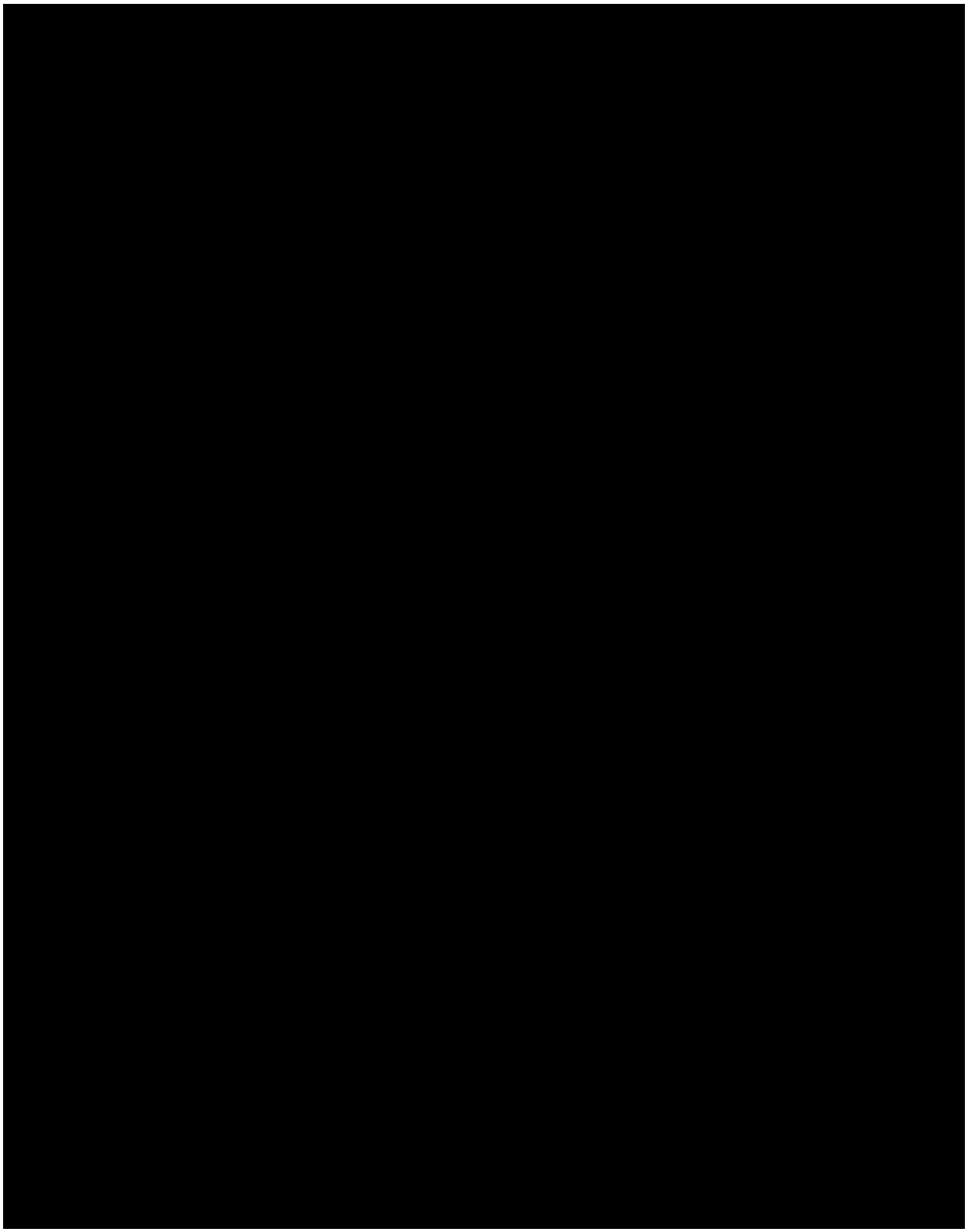
- For further methodological investigations**,** e.g. for stability testing, assessment of metabolites. However, only data related to the analyte and/or its metabolite(s) including anti-drug antibodies (if applicable) will be generated by these additional investigations

[redacted]

- For analyses of the concentrations of BI 730357 and its metabolites

Results of further investigations are not planned to be part of the trial report; however, results of further investigations may be part of the trial report, if required.

The study samples will be discarded after completion of the additional investigations, but not later than 5 years after the CTR is archived.



[redacted]

5.4.2 Pharmacodynamic biomarkers

Not applicable.

5.5 BIOBANKING

Not applicable.

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 Section 5.3 are generally used assessments of drug exposure. The biomarkers outlined in Sections 5.4 are of exploratory nature, only.

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 are to be performed and completed within a 2h-period prior to the next trial drug administration, if not indicated otherwise in the FlowChart.

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

Following administration of trial drugs 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 and ± 45 minutes from 28 hours onwards.

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

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

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

For cocktail PK blood sampling on Day 7 of Visit 2 and Days 6 and 8 of Visit 3, respectively, 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

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

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

[redacted]

6.2.2 Treatment periods

Each subject is expected to participate in 2 treatment periods (Days -1 to 7 in period 1 and Days -7 to Day 8 in Period 2). In the 2nd treatment period ambulatory dosing of BI 730357 (300 mg bid) starts on Day -7 to achieve steady state of the perpetrator drug. [redacted] In the 2 treatment period twice daily dosing of BI 730357 is continued until Day 6.

In the evening of Day -1 of each treatment period, study participants will be admitted to the trial site and kept under close medical surveillance for at least 60 hours. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. On all other study days, subjects will be treated in an ambulatory fashion.

For details on time points and procedures for BI 730357 dosing, collection of plasma and urine samples for PK analysis, refer to the Flow Chart and Section 5.3.2.

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

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the follow-up period, see Sections 5.2.2 to 5.2.5.
Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoTrial Visit.

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The main objective of this trial is to investigate the pharmacokinetics of digoxin, furosemide, metformin and rosuvastatin given as a cocktail alone (Reference, R) and as a cocktail together with BI 730357 (Test, T) following oral administration on the basis of the primary and secondary pharmacokinetic endpoints, as listed in Sections 2.1.2 and 2.1.3. The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of a linear model for logarithmically transformed PK endpoints.

[redacted]

7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of digoxin, rosuvastatin, metformin and furosemide (the cocktail) given alone compared with a combined administration with BI 730357 will be estimated by the ratios of the geometric means (test/reference) for the primary and secondary PK endpoints and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

7.3 PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who signed informed consent and were treated with at least one dose of study drug. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary or secondary 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/she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.

[redacted]

Adherence to the protocol will be assessed by the trial team. Important protocol deviations (iPD) categories will be suggested in the TSAP; iPDs will be identified no later than in the Report Planning Meeting, and iPD categories will be updated as needed.

Pharmacokinetics

The pharmacokinetic parameters listed in Sections 2.1 [redacted] will be calculated according to the relevant SOP of the Sponsor (001-MCS-36-472).

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

Relevant protocol deviations may be

- Incorrect dose of trial medication taken
- Use of restricted medications

Plasma and urine 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 is >5% C_{max} value of that subject
- Missing samples/concentration data at important phases of PK disposition curve

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

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

7.3.1 Primary endpoint analyses

Primary analyses

The primary endpoints are specified in Section 2.1.2. The analysis will be based on the PKS and will be descriptive in nature.

The statistical model used for the analysis of the primary endpoints $AUC_{0-\infty}$ and C_{max} of each of the variables rosuvastatin, digoxin, metformin and furosemide 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 the effect 'treatment' will be considered as fixed. The model is described by the following equation:

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

y_{km} = logarithm of response measured on subject m receiving treatment k,
μ = the overall mean,
π_k = the k^{th} treatment effect, k = 1, 2,
s_m = the effect associated with the m^{th} subject, m = 1, 2, ..., 15
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

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

[redacted]

[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 7.2) will be included in the safety analysis. Safety analyses will be descriptive in nature and based on BI standards. No hypothesis testing is planned.

For all analyses, the treatment actually administered (= treatment at onset of AE) to the subject will be used (any deviations from the planned 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 trial medication intake and end of REP (see Section 1.2.3) will be assigned to the treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. In case of two or more treatments, the follow-up will be summarized according to the previous treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before final database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity, and causal relationship of AEs will be tabulated by treatment, system organ class, and preferred term. SAEs, AESIs (see Section 5.2.5.1), and other significant AEs (according to ICH E3) will be listed separately.

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

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

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

Relevant ECG findings will be reported as AEs.

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

This is a non-randomised trial.

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 15 subjects in the trial, because this sample size is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (test/reference) can be expected with 95% probability. Precision is defined as the ratio of upper CI limit to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

[redacted]

For various assumptions around the gCV of 30% , Table 7.7: 1 provides an overview of the achievable precision for estimating the ratio of geometric means (test/reference). For illustrative purposes, the expected 90% confidence intervals are displayed for different values of the ratios T/R of geometric means.

Table 7.7: 1 Precision that can be expected with 95% probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a 2-period fixed-sequence trial *(N=15)*

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
20.0	1.18	100	84.73	118.02
20.0	1.18	150	127.10	177.03
20.0	1.18	200	169.47	236.04
25.0	1.23	100	81.39	122.87
25.0	1.23	150	122.08	184.31
25.0	1.23	200	162.77	245.74
30.0	1.28	100	78.23	127.83
30.0	1.28	150	117.34	191.75
30.0	1.28	200	156.45	255.67
35.0	1.33	100	75.25	132.89
35.0	1.33	150	112.87	199.34
35.0	1.33	200	150.50	265.78

*Ratio of geometric means (test/reference) for a PK endpoint is defined by $\exp(\mu_T)/\exp(\mu_R)$.

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

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

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

The calculation was performed as described by Julious [R11-5230] using R Version 3.6.1.

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

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

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

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

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

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

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

8.6 TRIAL MILESTONES

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

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

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

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

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

The EC/competent authority 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 [redacted], under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

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

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

The trial medication (BI 730357) will be provided by the [redacted]. Digoxin, rosuvastatin, metformin and furosemide will be purchased by the clinical site at a public pharmacy.

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

The analyses of digoxin, furosemide, metformin, rosuvastatin and cimetidine concentrations in plasma and urine will be performed under the responsibility of the Department of [redacted]

[redacted] at contract research organisations (CROs) [redacted]

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

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

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

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10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		01 October 2020
EudraCT number **EU number**		2020-003097-46
BI Trial number		1407-0038
BI Investigational Medicinal Product(s)		BI 730357
Title of protocol		The effect of BI 730357 on the pharmacokinetics of rosuvastatin, digoxin, metformin and furosemide given as a cocktail – an open-label, non-randomised, 2-period fixed-sequence trial in healthy subjects
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed	Flow Chart	Column “Safety laboratory”
	Flow Chart	Column “Planned time”
	Flow Chart	Foot note Section
	4.1.4	Drug assignment and administration of doses for each subject
	5.2.3	Safety laboratory parameters
	5.3.2	Methods of sample collection
	5.3.2.1	Blood sampling for pharmacokinetic analysis (cocktail components)
	5.3.2.3	Urine sampling for pharmacokinetic analysis
	[redacted]	
	6.1	Investigational plan
Description of change	Flow Chart	Clarified timepoint where safety lab is taken relative to breakfast
	Flow Chart	Corrected one value in the “planned time” column
	Flow Chart	[redacted]
	4.1.4	Clarified the allowed time period (2 min) for intake of cocktail probes
	5.2.3	[redacted] clarified that safety lab B may taken under non-fasted condition

	5.3.2	Anticoagulant blood drawing tubes have been changed into K_2-EDTA
	5.3.2.1	Deleted “and analyses”; further: Clarified that the primaries will be sent in two shipments
	5.3.2.3	[redacted] Clarified that the primaries will be sent in two shipments
	[redacted]	
	6.1	Added time tolerances for study procedures
Rationale for change	Flow Chart	To Clarify that safety lab B may be taken under non-fasted condition
	Flow Chart	Incorrect planned time
	Flow Chart	Clarification of logistical aspects to facilitate study conduct
	4.1.4	Clarification of logistical aspects to facilitate study conduct
	5.2.3	[redacted] Further, to clarify that safety lab B may be taken under non-fasted condition
	5.3.2	Availability of collection tubes
	5.3.2.1	There is no need to wait for the analyses of primaries before shipping backup samples since the primary aliquots contain enough material; further: To increase sample safety, primaries will be shipped in two shipments
	5.3.2.3	[redacted] further: There is no need to wait for the analyses of primaries before shipping backup samples since the primary aliquots contain enough material; [redacted] further: To increase sample safety, primaries will be shipped in two shipments
	[redacted]	
	6.1	To facilitate study setup and conduct

11.2 GLOBAL AMENDMENT 2

Date of amendment		19 October 2020
EudraCT number **EU number**		2020-003097-46
BI Trial number		1407-0038
BI Investigational Medicinal Product(s)		BI 730357
Title of protocol		The effect of BI 730357 on the pharmacokinetics of rosuvastatin, digoxin, metformin and furosemide given as a cocktail – an open-label, non-randomised, 2-period fixed-sequence trial in healthy subjects
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed	5.2.3	Safety laboratory parameters
Description of change	5.2.3	Described that safety lab B may be split (blood sampling for lymphocyte differentiation later on the same day) for logistical reasons (sample stability)
Rationale for change	5.2.3	Purely logistical step to ensure sample stability for lymphocyte differentiation which cannot be performed by the safety lab on Sundays. No impact on subjects' safety is foreseen thus this change is non-substantial from a regulatory view point.

APPROVAL / SIGNATURE PAGE

Document Number: c32357152 **Technical Version Number:3.0**

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

Title: The effect of BI 730357 on the pharmacokinetics of rosuvastatin, digoxin, metformin and furosemide given as a cocktail – an open-label, non-randomised, 2-period fixed-sequence trial in healthy subjects

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
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Approval-Team Member Medicine		20 Oct 2020 13:17 CEST
Author-Trial Clinical Pharmacokineticist		20 Oct 2020 13:19 CEST
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(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed