Clinical Trial Protocol

Document Number:		c42374778-02
EudraCT No. EU Clinical Trial No.	2023-506083-13-00	
Universal Trial No.	U1111-1293-6879	
BI Trial No.	1366-0055	
BI Investigational Medicinal Product	BI 685509	
Title	Randomised, double-blind, placebo-controlled and parallel group trial to investigate the effects of one dose (up-titration to a fixed dose regimen) of oral BI 685509 on portal hypertension after 8 weeks treatment in patients with clinically significant portal hypertension (CSPH) in decompensated cirrhosis after their first decompensation event, who are stabilized CTP 5-7	
Lay Title	A study to test whether BI 685509 helps people with liver cirrhosis and high blood pressure in the portal vein (main vessel going to the liver) who had bleeding in the esophagus or fluid accumulation in the belly	
Clinical Phase	II	
Clinical Trial Leader	[redacted]	
Coordinating Investigator		
Current Version and Date	Final Version 2.0 29 Nov 2023	
Original Protocol Date	07 Jul 2023	Page 1 of 98

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original Protocol date Latest revision date	07 Jul 2023 29 Nov 2023
BI trial number EU CT number Universal trial number	1366-0055 2023-506083-13-00 U1111-1293-6879
Title of trial	Randomised, double-blind, placebo-controlled and parallel group trial to investigate the effects of one dose (up-titration to a fixed dose regimen) of oral BI 685509 on portal hypertension after 8 weeks treatment in patients with clinically significant portal hypertension (CSPH) in decompensated cirrhosis after their first decompensation event, who are stabilized CTP 5-7
Coordinating Investigator	[redacted]
Trial sites	Multi-center trial
Clinical phase	II
Trial rationale	In this Phase 2 trial, the efficacy of treatment in patients with CSPH in decompensated cirrhosis after their first decompensation event due to non-cholestatic liver disease will be assessed. The trial will evaluate the short-term efficacy of BI 685509, where patients will be treated for 8 weeks and the portal pressure will be assessed quantitatively via HVPG measurements. The trial will also provide supportive evidence for the planned Phase 2I development.
Benefit-risk assessment and ethical considerations	Trial participants with cirrhosis with PH might benefit from the combined anti-fibrotic and hemodynamic effects of sGC activation. Treatment with BI 685509 in trial participants, who already developed decompensated cirrhosis will potentially result in the secondary prevention of related complications including further decompensation (variceal bleeding, ascites and encephalopathy), transplantation, or liver-related death. The potential risks, as described above, will be minimised by close monitoring of trial participants, by excluding at-risk trial participants from the trial, and by involvement of a DMC. Hepatic injury will also be assessed by an independent AC for safety purposes. Hence, overall, in the

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	context of the unmet medical need, the anticipated effects of BI 685509 on CSPH in trial participants with decompensated cirrhosis due to non-cholestatic liver diseases based on the safety profile of BI 685509, the benefit-risk evaluation of the compound is considered favourable for the intended population.
Trial objectives	The trial will investigate the safety and tolerability, of BI 685509, on top of standard of care, on portal hypertension in patients with clinically significant portal hypertension in decompensated cirrhosis after their first decompensation event. The primary objective is to estimate the percentage change in HVPG from baseline measured after 8 weeks in patients with decompensated cirrhosis.
Trial endpoints	The primary endpoint is the percentage change in HVPG from baseline (measured in mmHg) after 8 weeks of treatment. Secondary endpoints include: • Occurrence of a response, which is defined as > 10% reduction from baseline HVPG (measured in mmHg) after 8 weeks of treatment • Occurrence of one or more decompensation events (i.e. ascites, variceal haemorrhage [VH], and / or overt hepatic encephalopathy [HE]) during the 8 week treatment period • Occurrence of CTCAE grade 3 (or higher) hypotension or syncope based on Investigator judgement, during the 8 week treatment period • Occurrence of discontinuation due to hypotension or syncope during the 8 week treatment period
Trial design	Randomised, double-blind, parallel group, placebo-controlled comparison of treatment with BI 685509 over 8 weeks
Total number of trial participants randomised	Approximately 40
Number of trial participants per treatment group	Approximately 20
Diagnosis, main inclusion and exclusion criteria	Patients with CSPH in decompensated cirrhosis due to non-cholestatic liver disease after their first decompensation event (variceal haemorrhage or first event of clinically significant ascites), who are stabilized (CTP 5-7) Main Inclusion criteria: 1. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial

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	2. Male or female who is ≥ 18 (or who is of legal age in countries where that is greater than 18) and ≤ 75 years old at screening (Visit 1a) 3. Diagnosis of cirrhosis due to non-cholestatic liver disease (including HCV, HBV, NASH, alcohol-related liver disease, autoimmune hepatitis, Wilson's disease, haemachromatosis, alpha-1 antitrypsin [A1At] deficiency) 4. One previous clinically significant decompensation event with clinical resolution at least 4 weeks prior start of screening (visit 1a): a. First variceal haemorrhage b. First episode of clinically significant ascites (requiring intervention in lifestyle [fluid and salt restriction] or medical treatment) 5. Willing and able to undergo HVPG measurements per protocol (based on Investigator judgement) Main exclusion criteria: 1. History of cholestatic chronic liver disease (e.g. primary biliary cholangitis, primary sclerosing cholangitis) 2. Trial participants without adequate treatment for HBV, HCV or NASH as per local guidance (e.g. antiviral therapy for chronic HBV or HCV infection or lifestyle modification in NASH) 3. If received curative anti-viral therapy for HCV, SVR sustained for less than 1 years prior to screening 4. If receiving anti-viral therapy for HBV, less than 6 months on a stable dose prior to screening, with planned dose change during the trial or HBV DNA detectable 5. Weight change ≥ 5% within 6 months prior screening in patients with NASH 6. Must take, or wishes to continue the intake of, restricted concomitant therapy (refer to Section 4.2.2.1) or any concomitant therapy considered likely (based on Investigator judgement) to interfere with the safe conduct of the trial 7. SBP < 100 mmHg or DBP < 70 mmHg at screening (Visit 1a)

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	8. Hepatic impairment defined as a Child-Turcotte-Pugh score ≥8 at screening
Trial intervention and test product	BI 685509
Dose and mode of administration	[redacted]
Comparator product(s)	Placebo
Dose and mode of administration	Matching
Duration of treatment	8 weeks
Statistical methods	For the primary endpoint, an analysis of covariates (ANCOVA) model will be used to obtain adjusted means for the treatment effects. This model will include treatment, use (or not) of NSBBs or carvedilol and type of first decompensation event as a fixed classification effect and baseline HVPG as a linear covariate. The random error is assumed to be normally distributed with mean 0 and variance σ^2. The analysis will only be used for estimation of treatment effects without hypothesis testing. Secondary and further endpoints will be analysed descriptively. Safety analyses will be performed using BI standards and will be descriptive in nature.

FLOW CHART

Trial Periods	Screening[1]		Randomised Treatment						Follow-Up
Visit	1a[1]	1b[1]	2[2]	3	4	5	6	EoT / ED[3]	EoS[3]
Week	-4		R	1	2	4	6	8	10
Day	-28		1	8	15	29	43	57	71
Time window for visits (days)	See footnote 1		N/A	+ 2	+ 2	+ 2	± 3	± 5	± 5
Fasting status[4]	NF	F	F	NF	NF	F	NF	F	F
Informed consent	x								
Register patient in IRT system via IRT call	x								
Demographics[5]	x								
Medical history / baseline conditions[5]	x								
Concomitant therapy	x	x	x	x	x	x	x	x	x
Anthropometric measures[6]	x		x	x	x	x	x	x	x
Vital signs[7]	x		x[21]	x[21]	x[21]	x[21]	x	x	x
Physical examination[8]	x[20]		(x)	(x)	(x)	(x)	(x)	x	(x)
Resting 12-lead ECG[7]	x		x[21]	x[21]	x[21]	x[21]	x	x	x
Safety laboratory sampling	x		x	x	x	x		x	x
Pregnancy testing[9]	x_s		x_u			x_u		x_u	x_u
Hepatic venous pressure gradient (HVPG)[10]		x						x	
Ultrasound (liver and spleen)[11]		x				x		x	x
[redacted]		[redacted]				[redacted]		[redacted]	[redacted]
Review of in-/exclusion criteria	x	x	x						
Randomisation			x						

FLOW CHART cont.

Trial Periods	Screening[1]		Randomised Treatment						Follow-Up
Visit	1a[1]	1b[1]	2[2]	3	4	5	6	EoT / ED[3]	EoS[3]
Week	-4		R	1	2	4	6	8	10
Day	-28		1	8	15	29	43	57	71
Time window for visits (days)	See footnote 1		N/A	± 2	± 2	± 2	± 3	± 5	± 5
Fasting status[4]	NF	F	F	NF	NF	F	NF	F	F
IRT call			x	x	x	x	x	x	
Dispense trial medication			x	x	x	x	x		
Dose-titration[13]			x	x	x				
Train patient (home BP and HR monitoring)[14]			x	(x)					
Home BP and HR monitoring (by trial participant)[14]			x	→	→	→	→	→	→
Train / dispense / review trial participant reminder card[15]			x	x	x	x	x	x	
[redacted]			[redacted]			[redacted]		[redacted]	
Biobanking sampling[18]			x					x	
All AEs / SAEs / AESIs[19]	x	x	x	x	x	x	x	x	x
Collect returned trial medication				x	x	x	x	x	
Compliance check				x	x	x	x	x	
End of trial medication								X[22]	
Completion of trial participant participation									x

Footnotes:

1. The screening period consists of 2 visits (Visits 1a/b). These visits should ideally be completed within a period of 4 weeks. There is no minimum duration. A trial participant can proceed from one visit to the next as soon as all results from the previous visit are available and if he / she remains eligible for the trial. Refer to Sections 5.1.2, 5.2.5.1, 5.2.5.2 and 6.2.1
2. Visit 2 = enrolment / randomisation / Day 1 of trial medication. All assessments at this visit (excluding post-dose ECGs [redacted] [refer to Sections 5.2.4, 6.2 and Appendix 10.1]) should be completed before the first dose of trial medication is administered
3. Trial participants who complete 8 weeks of treatment will have an End of Treatment (EoT) visit, followed 2 weeks later by an End of Study (EoS) visit. The last dose of trial medication will be administered in the evening of the day before the EoT visit. Trial participants who discontinue trial medication prematurely will have an Early Discontinuation (ED) visit completed instead of the planned treatment period visit. The ED visit should be performed within 7 days of discontinuing the trial medication, followed 2 weeks later by an EoS visit. Refer to Section 6.2.2.1 for details of assessments that should be performed during an ED visit and the EoS visit that follows it.
4. Fasting status: F = fasting (i.e. overnight fast, no food or drink, except water), NF = non-fasting
5. For further details refer to Section 6.2.1
6. Anthropometric measures = height (measured at Visit 1a only), weight, and waist and hip circumference. Refer to Section 5.2.1.1
7. Measurement of vital signs should precede the 12-lead ECG, and measurement of the 12-lead ECG should precede blood sampling and intake of trial medication at visits where a single ECG is required. The 12-lead ECG should be performed after the trial participant has rested for at least 5 minutes in a supine position. From Visit 2 onwards, the trial participants home BP monitoring equipment should be used in the clinic to measure vital signs (refer to Sections 5.2.2, 5.2.2.1 and 5.2.4)
8. At Visits 1a and at the EoT / ED visit, a complete physical examination is required. At all other marked visits, a physical examination is only required if the trial participant reports symptoms. Refer to Section 5.2.1
9. Pregnancy testing required in women of child-bearing potential (WOCBP) only. x_s = serum testing; x_u = urine testing. Serum pregnancy will be done at screening (Visit 1a) and as a reflex when urine testing is positive. More frequent pregnancy testing should be done if required by local regulation and /or authority or per investigator judgement. Pregnancy testing at dosing visits should be completed prior to administration of trial medication. Refer to Section 5.2.3
10. For further details regarding the HVPG measurement, refer to Section 5.1.1
11. For further details regarding ultrasound of the liver and spleen, refer to Section 5.2.5.1

[redacted]

14. Electronic home BP monitoring equipment will be provided for a patient to measure BP and HR on a daily basis from Visit 2 (refer to Section 5.2.2.1). Following training on the use of the equipment at Visit 2, subsequent refresher training should be provided if required

[redacted]

17. [redacted]
18. Biobanking sampling requires a consistent status from one sample to another in terms of fasting vs non-fasting; a fasting status is therefore defined. Sampling is optional and requires separate informed consent. Refer to Section 5.5
19. After the EoS visit (= individual trial participants end of the trial) the Investigator should report only the following: any cancers of new histology and exacerbations of existing cancer, trial medication related Serious Adverse Events (SAEs) and trial medication related Adverse Events of Special Interest (AESIs) of which the Investigator may become aware of. These should be reported only via the BI SAE form (refer to Section 5.2.6.2.1)
20. The physical examination at Visit 1a should include an assessment of the clinical criteria for Child-Turcotte-Pugh classification (refer to Appendix 10.3)

21. During the dose-titration period (i.e. when up-titration is occurring), and at the subsequent visit, vital signs and 12-lead ECGs will also be repeated approximately 1 hour and 2 hours after intake of the trial medication. Measurement of vital signs should precede the 12-lead ECG, and measurement of the 12-lead ECG should precede the 1 hour and [redacted] (refer to Sections 5.2.2, 5.2.4 and 5.3).
22. Last trial dose will be administered at home the evening prior to the EoT visit.

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[redacted]

ABBREVIATIONS AND DEFINITIONS

[redacted]

AC	Adjudication Committee
ADME	Absorption Distribution Metabolism Excretion
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ANCOVA	Analysis of Covariance
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BDL	Bile Duct Ligation
BI	Boehringer Ingelheim
BID	bis in die (twice daily dosing)
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
BPM	Beats Per Minute
CA	Competent Authority

[redacted]

CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CI	Confidence Interval
C_{max}	Maximum measured concentration of the analyte in plasma
C_{pre}	Predose concentration of the analyte in plasma
CRA	Clinical Research Associate
CRO	Contract Research Organisation
CSPH	Clinically Significant Portal Hypertension
C_t	Concentration of the analyte in plasma at time t
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTP	*Child-Turcotte-Pugh score*

CV	Cardiovascular
DBL	Database Lock
DBP	Diastolic Blood Pressure
DDI	Drug-Drug Interaction
DILI	Drug Induced Liver Injury
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
DM	Diabetes Mellitus
DN	Diabetic Nephropathy
DNA	Deoxyribonucleic Acid
DSI	Disease Severity Index
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
ED	Early Discontinuation
ELF	Enhanced Liver Fibrosis
EoS	End of Study (corresponds with End of Trial)
EoT	End of Treatment
ES	Enrolled Set
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAS	Full Analysis Set
[redacted]	
FDA	Food and Drug Administration
FHVP	Free Hepatic Venous Pressure
[redacted]	
FPG	Fasting Plasma Glucose
FPI	Fasting Plasma Insulin
GCP	Good Clinical Practice
HA	Hyaluronic Acid
HbA1c	Hemoglobin A1c
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High-density Lipoprotein

HE	Hepatic Encephalopathy
HERG	Human Ether-a-go-go Related Gene
HFrEF	Heart Failure with reduced Ejection Fraction
HIV	Human Immunodeficiency Viruses
HR	Heart Rate
HVPG	Hepatic Venous Pressure Gradient
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICM	Iodinated Contrast Material
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
iSTAT	Independent Statistician
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IVC	Inferior Vena Cava
LDL	Low-density Lipoprotein
LPLT	Last trial participant last treatment
LSM	Liver Stiffness Measurement
MedDRA	Medical Dictionary for Drug Regulatory Activities
MELD	Model for End-stage Liver Disease
MI	Myocardial Infarction
[redacted]	
MMRM	Mixed Model with Repeated Measurements
MRD	Multiple Rising Dose
MRI	Magnetic Resonance Imaging
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
NO	Nitric Oxide
NSBB	Non-Selective Beta-Blocker
NYHA	New York Heart Association

OATP	Organic Anion Transporting Polypeptide
[redacted]	
PD	Pharmacodynamic
PDE	Phosphodiesterase
PG	Pharmacogenomic
[redacted]	
PK	Pharmacokinetics
PH	Portal Hypertension
[redacted]	
PV	Pharmacovigilance
QD	Quaque Die (once a day)
REML	Restricted Maximum Likelihood
REP	Residual effect period
RNA	Ribonucleic Acid
RPM	Report Planning Meeting
RS	Randomised Set
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
sGC	soluble Guanylate Cyclase
SOP	Standard Operating Procedure
SSc	Systemic Sclerosis
SUSAR	Suspected Unexpected Serious Adverse Reactions
SVR	Sustained Virological Response
TID	Ter in Die (three times a day)
[redacted]	
T_{max}	Time from dosing to maximum measured concentration of the analyte in plasma
TS	Treated Set
TSAP	Trial Statistical Analysis Plan

UGT	Uridine Glucuronyl Transferase
ULN	Upper limit of normal
US	Ultrasound
VAS	Visual Analogue Scale
VCTE	Vibration Controlled Transient Elastography
VH	Variceal Haemorrhage
WHO	World Health Organisation
WHVP	Wedged Hepatic Venous Pressure
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Cirrhosis is the end-stage liver condition caused by multiple chronic diseases, like hepatitis C virus infection (HCV), chronic alcohol abuse, or metabolic syndrome with non-alcoholic fatty liver disease (NAFLD). Cirrhosis by itself is a chronic condition with a high mortality. It is a heterogenous disease that is classified into two main prognostic stages: compensated and decompensated cirrhosis. This classification depends on the presence or absence of clinically evident decompensating events (specifically ascites [more than perihepatic ascites], variceal haemorrhage (VH) and / or apparent hepatic encephalopathy (HE) [P18-02639]). Currently, there is no treatment available for cirrhosis for reduction of fibrotic tissue or regeneration of hepatocytes. The main treatment goal is to delay decompensation, improve quality of life, and treat the symptoms of cirrhosis and especially decompensation.
Portal hypertension (PH) is the initial and main consequence of cirrhosis and is responsible for the majority of its complications [R17-1181, P18-02639]. The only currently recommended clinical approaches to prevent PH-related decompensating events in patients are endoscopic variceal ligations or off-label use of non-selective beta-blockers (NSBBs) or carvedilol for primary and secondary prophylaxis of variceal bleeding. However, not all patients with PH achieve a hemodynamic response with these current treatment options. NSBBs and carvedilol are currently used to prevent complications of cirrhosis and improve survival in patients, but these benefits only occur in less than half of patients treated, and mostly in those who achieve a significant decrease in portal pressure. An unmet need remains for a substantial number of patients who cannot tolerate treatment with NSBBs or carvedilol due to decreased systemic blood pressure (BP) and heart rate (HR), and who have a higher risk for further progression and decompensation.

Therefore, there is an existing unmet medical need to reduce portal pressure and improve liver perfusion in this population of patients with PH and especially clinically significant portal hypertension (CSPH). CSPH is associated with an increased risk of developing varices, overt clinical decompensation (ascites, VH, and HE), postsurgical decompensation, and hepatocellular carcinoma [R18-2743, R20-1200, P18-02639].

1.2 DRUG PROFILE – BI 685509

As a primary indication, the development of BI 685509 by Boehringer Ingelheim (BI) is intended for slowing progression of renal damage and reduction of cardiovascular events in patients with chronic kidney disease. Additional intended indications are the treatment of CSPH in patients with compensated cirrhosis due to non-cholestatic liver disease and systemic sclerosis (SSc).

1.2.1 Key characteristics of BI 685509

Mode of action

BI 685509 is a nitric oxide (NO)-independent activator of soluble guanylate cyclase (sGC), which increases production of cyclic guanosine monophosphate (cGMP). cGMP is a potent mediator of vasorelaxation, an inhibitor of platelet aggregation and inflammation, and is also crucial for proper endothelial function in the vascular bed (increased sinusoidal lumen and perfusion). Accordingly, BI 685509 with its sGC-cGMP mediated mechanism of action, is considered an appropriate treatment option for CSPH and prevention of decompensation in patients with compensated cirrhosis. Additionally, unlike NSBBs / carvedilol, there is no concurrent reduction in systemic BP and HR expected, which might lead to better tolerability in chronic treatment. Further, cGMP also modulates liver fibrosis via inhibition of Transforming Growth Factor beta (TGFß) induced extracellular matrix production, fibroblast to myofibroblast differentiation and cell proliferation, and also promotes reduction of intra-hepatic resistance via inhibition of hepatic stellate cell activation and vasoconstriction. Thus, BI 685509, an sGC activator that increases production of cGMP, may have the potential to slow down or halt progression of further fibrogenesis, improving liver perfusion and reducing PH.

Key pharmacokinetic characteristics

The pharmacokinetics of BI 685509 is characterised by rapid absorption, reaching peak plasma concentrations between 0.5-1.0 hour post-dose in healthy volunteers. Thereafter, BI 685509 plasma concentrations decline in a biphasic manner. Systemic exposure to BI 685509 increased proportional to dose following administration of single doses, and close to dose-proportional exposure was observed at steady state for the dose range tested from [redacted] The single-dose and steady-state PK parameters (AUC0-∞ and AUC0-τ,ss) for BI 685509 were similar, suggesting linear PK with respect to time. Minimal amounts of BI 685509 were excreted unchanged in urine (< 1% of dose). The apparent terminal elimination half-life was approximately 9 to 15 hours. After multiple oral administration of qd or bid regimens, limited accumulation was observed and steady state appears to be attained by approximately 3 to 5 days after the start of multiple dosing.Following single and multiple oral administrations of BI 685509, the exposures of BI 685509 (Cmax and AUC) were comparable between Chinese and Japanese subjects but may be up to 2-fold higher compared to Caucasian subjects. This may be related to the smaller body weight in Asian subjects. Although exposures were higher in Asian subjects, there were no notable differences with respect to BP, HR and adverse events (AEs) between Asian and Caucasian subjects. This leads to the current assumption that no considerable dose adjustments are needed for Asian patients for the Phase 2 program that will recruit patients from Japan and other Asian countries.Based on the PK analysis of Trials 1366-0004 and 1366-0005, the exposure to BI 685509 observed in patients with diabetic nephropathy (DN) with an eGFR ranging from 16 – 95 mL/min/1.73 m^2 was slightly higher compared to exposure observed in healthy volunteers in Trial 1366-0003. Also, as observed in healthy volunteers, limited accumulation after multiple dosing was observed in patients with DN.A population PK model updated with data from 1366-0005 was used for simulations. Based on the population PK model, exposure ($AUC_{0\text{-}24,ss}$ and $C_{max,ss}$) was simulated for different eGFR ranges using the highest titrated dosing regimen to be investigated in this trial: [redacted] TID / [redacted] TID. Table 1.2.1: 1 provides the corresponding fold-change predictions of these PK

exposures for differing degrees of renal impairment relative to the median value simulated in healthy volunteers (eGFR ≥90 mL/min/1.73m^2). For patients with eGFR of 20 mL/min/1.73m^2 up to <90 mL/min/1.73m^2, the predicted median $AUC_{0\text{-}24,ss}$ is 9-59% higher, and the predicted median $C_{max,ss}$ is 10-28% higher in comparison to healthy volunteers. Although the model predicted $AUC_{0\text{-}24,ss}$ for patients with eGFR of 20 mL/min/1.73m^2 is ~ 1.6-fold higher compared to healthy volunteers, the projected increase in $C_{max,ss}$, a parameter which is closely associated with orthostatic dysregulation, is only marginal.

Table 1.2.1: 1 Fold-change in PK exposure predictions in renally impaired patients relative to the median predicted value in healthy volunteers (eGFR ≥90 mL/min/1.73m2) based on highest titrated dose of [redacted] BID at Day 56 / 8 weeks

Measure	eGFR	Median	2.5th	97.5th
$AUC_{0\text{-}24,ss}$	≥90	1.00	0.349	2.83
	60 – 90	1.09	0.431	2.76
	45 – 60	1.25	0.453	3.34
	30 – 45	1.37	0.536	3.79
	20 – 30	1.59	0.585	4.49
$C_{max,ss}$	≥90	1.00	0.379	2.39
	60 – 90	1.10	0.437	2.75
	45 – 60	1.15	0.445	2.71
	30 – 45	1.16	0.469	2.84
	20 – 30	1.28	0.539	3.17

Source: c35011958

Based on the PK of hepatically impaired patients in Trial 1366-0020, the exposure observed in hepatic impairment patients increased with increasing dose. After single and multiple oral administrations, the exposure in Child-Turcotte-Pugh A patients was comparable to Child-Turcotte-Pugh B patients. In Child-Turcotte-Pugh A patients, the steady state exposures of [redacted] BID regimen (dose group 3) with last dose of [redacted] QD was 150 nmol/L Cmax,ss, and 729 nmol*h/L AUC0-tau,ss, thus yielding an estimated total daily exposure of ~1460 nmol*h/L. In Child-Turcotte-Pugh B patients, the exposures associated with the same dosing regimen was 122 nmol/L Cmax,ss, and 604 nmol*h/L AUC0-tau,ss, yielding an estimated total daily exposure of ~1210 nmol*h/L [c34995868-01]. The exposure observed in the [redacted] BID dosing regimen in hepatic impaired patients were comparable to that of the [redacted] dosing regimen in healthy volunteers (Trial 1366-0003) and patients with DN (Trial 1366-0004).BI 685509 was generally safe and well tolerated in patients with DN in phase 1 Trial 1366-0004 and phase 2 Trial 1366-0005 with eGFR 20 – 90 mL/min/1.73m^2 and in hepatically impaired Child-Turcotte-Pugh A and B patients in Trial 1366-0020. The adverse events reported so far are anticipated from the mode of action of BI 685509 or can be attributed to the studied condition or concomitant diseases. A similar titration regimen will be used in this trial compared to Trial 1366-0020 which will help detect any orthostatic dysregulation and allow adjustment of doses accordingly (refer to Section 4.1.4).Drug interactions

The combination of BI 685509 with other compounds involved in the NO-sGC-cGMP pathway, such as NO-donors (e.g. nitrates), phosphodiesterase (PDE)-5- inhibitors, non-specific PDE inhibitors and sGC-simulators might further increase the risk for hypotensive episodes and potentially reactive HR increases and the severity of these effects. Based on *in*

vitro data, BI 685509 is a weak inactivator of CYP3A4 and CYP2C8. A Drug-Drug Interaction (DDI) potential with CYP3A4 substrates cannot be excluded as BI 685509 is predicted to be a weak CYP3A4 inactivator. DDI threshold dose for CYP2C8 inactivation for CSPH indication is close to clinically relevant dose tested in phase 2. Thus, in addition to close monitoring of adverse events among patients taking CYP3A4 narrow therapeutic index/or sensitive substrates, CYP2C8 and CYP3A4 narrow therapeutic index/or sensitive substrates would also be monitored to support patient safety. Inhibitors of UGT (uridine glucuronyl transferase) enzymes (especially UGT1A1) may potentially impact BI 685509 exposures in a clinically relevant manner. BI 685509 is a substrate of P-gp (permeability glycoprotein) and OATP (organic anion transporting polypeptide)1B1/3 transporters. Co-administration of single doses of BI 685509 and the P-gp inhibitor itraconazole increased BI 685509 C_{max} approximately 1.35-fold and AUC_{0-tz} approximately 1.55-fold, which is considered not clinically relevant. OATP1B1/3 inhibition by rifampicin increased the exposure of BI 685509 after co-administration of single doses approximately 2.15-fold for C_{max} and 2.74-fold for AUC_{0-tz}, which is considered clinically relevant. Thus, OATP1B1/3 inhibitors will be restricted (refer to Table 1.4.2: 1 and Section 4.2.2.1).

Residual Effect Period
The Residual Effect Period (REP) of BI 685509 is 7 days. This is the period after the last dose with measurable drug levels and / or pharmacodynamic (PD) effects still likely to be present.

1.2.2 Data from non-clinical studies

BI 685509 activates sGC-mediated cGMP production in the presence of plasma proteins in an assay using human or rat platelet-rich plasma with EC50 values of 371 nM and 304 nM, respectively. BI 685509 was tested in the bile duct ligation (BDL) rat model of cirrhotic PH in which the compound (3 mg/kg and 10 mg/kg) or vehicle were gavaged twice daily from weeks 2-4 after BDL. BDL rats presented with PH and prominent liver fibrosis. Compared to vehicle, portal pressure was significantly reduced with both doses of BI 685509 (-5.1 mmHg for 3 mg/kg, $p<0.001$ and -4.5 mmHg for 10 mg/kg, $p<0.01$), whereas no significant effect on HR and mean arterial pressure was observed. Both doses of BI 685509 significantly reduced both hepatic hydroxyproline content (-30% for 3 mg/kg, $p<0.05$ and - 32% for 10 mg/kg, $p<0.05$) and fibrotic area in chrome aniline-stained liver slices (-62% for 3 mg/kg, $p<0.001$ and -50% for 10 mg/kg, $p<0.01$). BI 685509 treatment resulted in reduced levels of liver transaminases and direct target engagement of the sGC pathway could be demonstrated. Based on portal pressure reduction and anti-fibrotic efficacy, the 3 mg/kg dose is considered as the effective dose since the 10 mg/kg dose did not provide better efficacy.

The major route of elimination for BI 685509 in rats is biliary excretion. More than 85% of the radioactivity was found in the faeces after oral and intravenous administration of [14C]BI 685509 to rats. [14C]BI 685509-derived radioactivity was well distributed to most tissues except for the central nervous system, white adipose, seminal vesicles, testis, eye lens, bone and skeletal muscle.

So far, the toxicity profile of BI 685509 has been assessed in safety pharmacology, genetic toxicity, repeat dose toxicity studies in rat and monkey and embryo-foetal development

studies in rats and rabbits. In general, BI 685509 appears to be safe at clinically relevant plasma exposures. Delayed gastric emptying and decreased intestinal transit might result in gastrointestinal side effects. Only in rats, mild to moderate renal pelvis inflammation was observed sporadically. This finding is deemed to be rat specific and related to the mechanism of action. It seems to be unlikely that related AEs like urinary tract infections will occur in human subjects. BP decreased dose dependently with compensatory increases in HR in respective studies in rats and monkeys. No effects on the central nervous system or the respiratory system were found in respective safety pharmacology studies. There were no BI 685509-related effects on embryo-foetal mortality, foetal growth or dysmorphology (malformations) in the embryo-foetal development studies. BI 685509 is considered non-genotoxic and with low risk for photo-toxicity. The proarrhythmic risk of BI 685509 due to effects on ventricular repolarisation is considered to be low.

1.2.3 Data from clinical studies

BI 685509 has been tested in a single rising dose trial, a food effect and DDI trial, two multiple rising dose (MRD) trials in male healthy volunteers, and one multiple oral rising dose trial in patients with DN. Overall, it was well tolerated except for dose limiting orthostatic dysregulation. In the single dose trials, BI 685509 appears to reduce diastolic and systolic BP with a compensatory increase in HR, however, up-titration and TID dosing markedly improved the cardiovascular tolerability of the drug.

Summary of data from Trial 1366-0020:
In the trial, 49 patients with hepatic impairment due to various underlying liver diseases were treated for up to 4 weeks (24 patients with cirrhosis Child-Turcotte-Pugh A and 25 patients with cirrhosis Child-Turcotte-Pugh B in patients with hepatic impairment, as these are the intented patient population). Doses up to [redacted] bid were used.

The treatment with BI 685509 in patients with cirrhosis of different aetiologies, with hepatic impairment with Child-Turcotte-Pugh A and B was safe and well-tolerated. All AEs were of mild or moderate intensity. No treatment-related SAEs, as defined by the Investigator, occurred, or led to treatment discontinuation. Orthostatic intolerance occurred in the higher dose groups, and did not lead to treatment discontinuation, but recovered during continued treatment. Treatment with BI 685509 had no effect on laboratory parameters, including liver enzymes and bilirubin.

An effect of BI 685509 on the predicted placebo-corrected mean change from baseline QTcF (ΔΔQTcF) was seen. In both patient groups, there was a dose dependent increase of ΔΔQTcF up to 13.7 ms, with the upper 90% CI > 20 ms. In one patient group (Child-Turcotte-Pugh A) this was concomitant with a change of the predicted placebo-corrected mean change from baseline heart rate (ΔΔHR) of > 10 beats per minute (bpm), but not in the other patient group [c34995868-01]. No such effect was seen in healthy Caucasian volunteers (Trial 1366-0003) for dosing regimens achieving exposure relevant for this trial. In healthy Asian volunteers (Trial 1366-0013), at a dose regimen achieving exposure relevant for this trial (i.e. starting dose of [redacted] TID up to a final dose of [redacted] TID), increase of ΔΔQTcF was seen up to 11.7 ms with 90% CI <20 ms, concomitant with an increase of ΔΔHR of nearly 10 bpm.

There is no known effect of BI 685509, nor its metabolite BI 685144, on hERG channel at plasma concentrations reached in the studies in humans, even considering the individual patients with highest C_{max}. BI 685509 and BI 685144 did not show inhibitory effects on other cardiac ion channels, including Nav1.5, Kv4.3, Cav1.2 and Kir 2,1, at tested concentrations providing approximately 100 folds to the C_{max} achieved in the clinical trials (please refer to IB [c02778238].

In addition to the safety and exposure, exploratory efficacy biomarkers were investigated in the Child-Turcotte-Pugh A patients. Considering the short treatment period, especially only 12 days on the maintenance dose, positive signals could be observed in the HepQuant® shunt fraction, which is a surrogate of the amount of blood shunted by the liver. A mean reduction of >10% could be observed in the two higest maintenance doses, and specifically in the highest dose group, all patients showed a reduction. [redacted] Further optimisation and training since the initial study will allow complete assessment of this novel technique during the current studies and will allow spleen stiffness to be used as a non-invasive biomarker for portal hypertension.

For a more detailed description of the BI 685509 profile, please refer to the current Investigator's Brochure [c02778238].

1.3 RATIONALE FOR PERFORMING THE TRIAL

In this Phase 2 trial, the efficacy of treatment in patients with CSPH (defined by HVPG ≥10 mmHg) in decompensated cirrhosis due to non-cholestatic liver diseases will be assessed. The trial will serve to evaluate short-term efficacy of BI 685509 and will also provide supportive evidence for the planned Phase 2I development together with trials 1366-0021 and 1366-0029. The data of this trial will be indirectly compared with the data from trials 1366-0021 and 1366-0029.

In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking (please see Section 5.5). If the patient agrees, banked samples may be used for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an adverse event (AE), or to gain a mechanistic understanding of drug effects and thereby better match patients with therapies.

1.4 BENEFIT - RISK ASSESSMENT

The overall safety profiles of BI 685509 is outlined in the current Investigator's Brochures (IB) [c02778238] .

1.4.1 Benefits

BI 685509 has demonstrated efficacy in pre-clinical models for cirrhosis and PH, supporting its potential for the treatment of PH and fibrosis. As cGMP elevation has been associated with anti-fibrotic, anti-proliferative and anti-inflammatory effects, pharmacological activators of sGC, like BI 685509, have the potential to slow down or halt complications of cirrhosis by reducing PH, improving liver perfusion, and potentially having beneficial effects on the cardiovascular system. This would not only improve clinical outcomes and quality of life for the patients, but would also reduce the need for invasive procedures and resources (pharmacological and non-pharmacological therapies, e.g. endoscopic variceal ligation, large volume paracentesis, albumin therapy, transjugular intra-hepatic portosystemic shunt [TIPS] and orthotopic liver transplantation), reduce overall morbidity and mortality, and improve survival [R19-3528, R20-1198, R20-1199]. BI 685509 is a new chemical entity within development however and an individual benefit cannot be guaranteed.

The monitoring that is planned as part of this trial, and the intensive medical care that patients will receive (e.g. imaging assessments, daily measurements of vital signs etc.), may also be beneficial. Furthermore, trial patients will have the opportunity to undergo HVPG measurement, the current gold standard to detect PH, which offers added prognostic value, a strong predictor of clinical decompensation. At present HVPG measurement is only available at selected sites due to its invasive nature and the need for skilled technical staff to carry out HVPG measurements.

1.4.2 Risks

Trial participants will be exposed to trial-related risks due to exposure to the investigational medicinal product (BI 685509), the trial procedures and other risks. For details refer to Tables 1.4.2: 1, 1.4.2: 2 and 1.4.2: 3 below.

Table 1.4.2: 1 Overview of trial related risks - investigational medicinal product (BI 685509)

Possible / known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Potential AEs such as hypotension / orthostatic dysregulation, tachycardia, peripheral oedema and gastrointestinal events such as diarrhoea, abdominal pain and nausea	Primarily related to the vasodilatory effects and subsequent reactions or gastrointestinal effects which are directly related to the mechanism of action	To minimise the risk of severe or serious side effects, participants of this trial will only be exposed to doses that have been safely administered to healthy volunteers and patients in the preceding trials (refer to the IB [c02778238] and Sections 1.2.1 and 4.1.2). All trial participants will be monitored for AEs, and BP and HR will be measured daily (by the trial participant at home) during the treatment period. Trial participants
		with oedema or gastrointestinal side effects will be managed by standard of care, and trial participants with a known history of orthostatic dysregulation and those with a SBP <100 mmHg or a DBP <70 mmHg will be excluded. In addition, up-titration to the maintenance dose within each treatment group will occur at weekly intervals in order to increase the tolerability of the trial medication with regards to cardiovascular effects.
Potential QT-interval prolongation	Refer to Section 1.2.3	Trial participants with long QT / QTcF-interval, trial participants with a family history of long QT syndrome, or those using concomitant therapies known to increase the risk of Torsade de Points will be excluded from the trial (refer to Sections 3.3.3 and 4.2.2.1). ECGs will be performed at each visit in the randomised treatment period of the trial, and trial medication will be discontinued in the event of a prolonged QT / QTcF-interval (refer to Section 3.3.4).

Table 1.4.2: 1 (cont.) Overview of trial related risks - investigational medicinal product (BI 685509)

Possible / known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Risks related to drug-drug interaction (DDI)	Refer to Section 1.2.1	Close monitoring of trial participants for AEs and restricted co-administration of impacted concomitant therapies such as treatments with a similar mechanism of action (i.e. activators of the NO-sGC-cGMP pathway), clinically relevant therapies inhibiting the activity of OATP1B1/3 and clinically relevant UGT inhibitors. Trial participants taking concomitant therapies that are sensitive CYP3A4 and CYP2C8 substrates and / or narrow therapeutic index CYP3A4 and CYP2C8 substrates will also be monitored closely. A list, to support the identification of the above-mentioned concomitant therapies at trial sites, will be provided in the Investigator Site File (ISF). Also refer to Sections 3.3.3 and 4.2.2.1.

Table 1.4.2: 2 Overview of risks – trial procedures

Possible / known risks of clinical relevance	**Summary of data, rationale for the risk**	**Mitigation strategy**
Potential risks associated with the HVPG measurement, which are almost exclusively related to the venous access, usually performed under local anaesthesia and sometimes mild sedation. Common side effects include those associated with procedural sedation (e.g. nausea, vomiting, aspiration pneumonia, irregular heartbeat, breathing difficulties), pain at the insertion site, or slight thoracic or abdominal discomfort when advancing the catheter through the vena cava system into the hepatic	The HVPG procedure is the gold standard to assess portal pressure quantitatively, but it is invasive, resource-intensive, and requires interventional skills and expertise in interpreting the reliability and plausibility of pressure readings (refer to Section 5.1.1). Hence, the procedure is not commonly performed as part of clinical practice. To date, there are no alternative, non-invasive parameters reflecting the degree of portal pressure with similar accuracy as HVPG. The complication rate of HVPG measurement is low, and the pressure measurement itself is not painful. Patients may be sedated if required (e.g. they are nervous) or based on defined standards. The procedure is performed using ultrasound-guidance,	Risks relating to HVPG measurements will be mitigated by conducting the trial at sites where the staff is experienced in / have access to a nearby site experienced in the procedure. Such sites will be familiar with preparing patients before the procedure, allaying any fears, and the subsequent patient monitoring that is required. This might include adequate hydration to help avoid e.g. contrast-induced renal injury, and educating patients

Table 1.4.2: 2 (cont.) Overview of risks – trial procedures

Possible / known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
vein and while inflating the balloon. Specific but rare complications related to the venous access include haematomas at the access site, pneumothoraces requiring a chest tube and cardiac arrhythmias [R20-3977]. Iodinated contrast material (ICM) also has the potential to cause hypersensitivity and can lead to contrast-induced renal injury	and under fluoroscopic control with use of ionising radiation and ICM. Radiation exposure is, in most cases, very limited and the effective dose received by patients (~ 5.4 mSv) is inferior to most diagnostic radiology examinations of the abdomen and similar to that of a plain X-ray of the upper gastrointestinal tract [R20-4181, R20-4191, R20-3299]. The volume of ICM used is in the region of 7 mL (R20-4181)	regarding symptoms suggestive of complications. Patients will be monitored for AEs, and those with contraindications to the procedure will be excluded. The burden of HVPG measurements on the patient will also be reduced as far as possible in terms of the chosen trial design (refer to Section 3.2)
Potential risks of blood sampling by venipuncture or through an indwelling catheter such as fainting, pain, bruising, swelling, or rarely, transient inflammation or infection where the needle is inserted. In rare cases a nerve may be damaged inducing long-lasting abnormal sensations (paraesthesia) or impaired sensation of touch and persistent pain	No health-related risk is expected from the total volume of blood withdrawn per patient during the trial. Blood sampling is a general risk, acceptable in the framework of clinical trial participation	Evaluation of the medical expertise of the trial sites will be part of the site feasibility assessment. In addition, and to ensure patient safety, all events or symptoms reported will be managed according to the judgement of the Investigator

Table 1.4.2: 3 Overview of risks – other risks and safety measures

Possible / known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Drug-induced liver injury (DILI)	A rare but severe event, thus under constant surveillance by Sponsors and regulators. No DILI cases have been observed in current BI 685509 clinical trials	This trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety. Removal and stopping criteria have also been defined, and there will be oversight of DILI by a Data Monitoring Committee (DMC). Hepatic injury will also be adjudicated by an independent adjudication committee (AC). Refer to Sections 3.2, 3.3.4, 5.2.5.2, 5.2.6.1.4, 8.7 and Appendix 10.2
Unintentional exposure of an embryo or foetus to trial medication	Based on the findings in pre-clinical studies conducted to date and in accordance with international regulatory guidelines, the inclusion of WOCBP in this trial is justified	To minimise the risk, WOCBP must agree to the requirements for pregnancy testing. Both WOCBP and men able to father a child (with a female sexual partner of CBP) must also agree to the contraceptive methods described (refer to Sections 3.3.2 and 4.2.2.3)

A Hepatic Injury Adjudication Committee (AC) and Data Monitoring Committee (DMC) independent from the sponsor will be established to review safety data at regular intervals. For further details see Section 8.7.

1.4.3 Discussion

The nature of the target and the mechanism of action of BI 685509 is well understood.
In the context of the unmet medical need and anticipated benefit of BI 685509, the benefit risk evaluation of the compound based upon the available preclinical and clinical information, is favourable.
Considering the medical need for the development of a better tolerated and more effective treatment for trial participants with CSPH in decompensated cirrhosis the expected benefit outweighs the potential risks.

Trial participants with cirrhosis with PH might benefit from the combined anti-fibrotic and hemodynamic effects of sGC activation (refer to Section 1.1). Treatment with BI 685509 in trial participants, who already developed decompensated cirrhosis will potentially result in the secondary prevention of related complications including further decompensation (variceal bleeding, ascites and encephalopathy), transplantation, or liver-related death. The potential risks, as described above, will be minimised by close monitoring of trial participants, by excluding at-risk trial participants from the trial, and by involvement of a DMC – refer to Sections 3.2 and 8.7. Hepatic injury will also be assessed by an independent AC for safety

purposes (refer to Sections 3.2, 5.2.5.2 and 8.7). Hence, overall, in the context of the unmet medical need, the anticipated effects of BI 685509 on CSPH in trial participants with decompensated cirrhosis due to non-cholestatic liver diseases based on the safety profile of BI 685509, the benefit-risk evaluation of the compound is considered favourable for the intended population.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The trial will investigate the safety and tolerability of BI 685509 in patients with CSPH in decompensated cirrhosis due to non-cholestatic liver diseases on top of standard of care. The primary objective is to estimate the percentage change in HVPG from baseline measured after 8 weeks in comparison to placebo. The primary analysis will be made for treated patients with baseline HVPG measurements (Full Analysis Set, FAS) as if all trial participants took treatment for the duration of the trial.

2.1.2 Primary endpoint

The primary endpoint is the percentage change in HVPG from baseline (measured in mmHg) after 8 weeks of treatment.

2.1.3 Secondary endpoints

Secondary endpoints include:

- occurrence of a response, which is defined as >10% reduction from baseline HVPG (measured in mmHg) after 8 weeks of treatment
- occurrence of further decompensation events (i.e. ascites, VH, and / or overt HE) during the 8-week treatment period
- occurrence of CTCAE grade 3 (or higher) hypotension or syncope based on Investigator judgement, during the 8-week treatment period
- occurrence of discontinuation due to hypotension or syncope during the 8-week treatment period

2.2 FURTHER OBJECTIVES AND FURTHER ENDPOINTS

2.2.1 Further objectives

In addition to the main objectives defined above, further objectives of this trial include an evaluation of general safety, [redacted]

2.2.2 Further endpoints

[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This phase 2 multi-national, randomised, placebo-controlled and parallel group trial to investigate the effects of oral BI 685509 on portal hypertension after 8 weeks treatment in patients with clinically significant portal hypertension (CSPH) in decompensated cirrhosis after the first decompensation event, who are stabilized (CTP 5-7).

Trial participants will be enrolled in the trial and screened for eligibility once they have signed the informed consent. The screening period consists of up to 2 visits (Visits 1a and b) and will last a maximum of 4 weeks. Trial participants will be able to progress from one visit to the next when eligibility of the previous visit is confirmed. Assessments will include ultrasound of the liver and spleen, [redacted] and measurement of HVPG. Trial participants who remain eligible and who successfully complete this period will proceed to the 8-week randomised, placebo-controlled treatment period.

In total, 40 trial participants will be randomized in a 1:1 ratio, with 20 trial participants in the active treatment arm, and 20 trial participants in the placebo arm. The randomization will be stratified by use (or not) of NSBBs / carvedilol and type of first decompensation event (ascites or variceal haemorrhage).

Following randomization at visit 2, trial participants will begin the intake of trial medication(s) and will enter a dose-titration period of BI 685509 or matching placebo. If the dose is tolerated, one week later (at Visit 3, day 8), the dose for all will be up-titrated to [redacted] BID 685509 or matching placebo. If this dose is tolerated, a second up-titration to [redacted] BID BI 685509 or matching placebo will occur after another week (at Visit 4, day 15). Following the dose-titration period, and if the dose is tolerated, trial participants will remain on the highest dose of BI 685509 for the remainder of the treatment period until they reach the End of Treatment (EoT) visit and 8 weeks of treatment. If the dose is not tolerated, trial medication may be interrupted or the dose can be reduced / down-titrated.

The ultrasound and [redacted], and the HVPG measurement will be repeated during the treatment period (refer to Figure 3.1: 1).

After the 8 week treatment period all trial participants will enter a 2 week follow-up period without trial medication. The trial participant's participation in the trial will be complete when they have performed the last planned visit (i.e. End of Study [EoS], 2 weeks after EoT).

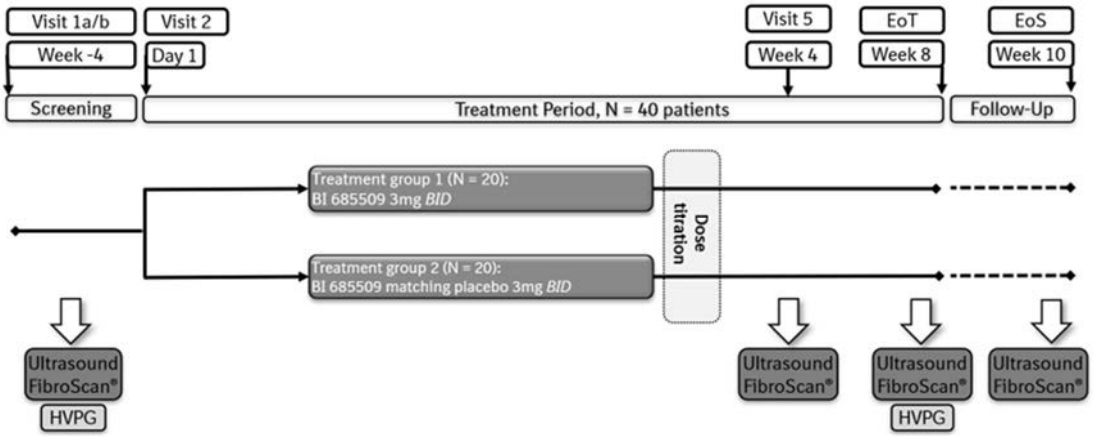


Figure 3.1: 1 Trial design schematic

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

A randomised, double-blind, placebo-controlled and parallel group design has been chosen for this trial, on top of standard of care. The randomised double-blind design will control for assignment bias. Placebo as control was chosen to show the efficacy of BI 685509 compared to placebo plus standard of care.

A treatment duration of 8 weeks has been chosen to allow an evaluation of short-term efficacy and indirect comparison to the week 8 results from trials 1366-0021 and 1366-0029.

The trial participant population of this trial has been chosen as it represents the intended patient population to be treated with for BI 685509 (patients with clinically significant portal hypertension in decompensated cirrhosis due to non-cholestatic liver diseases).

For details regarding the choice of renal function in the patient population, refer to Section 1.2.

The measurement of HVPG was chosen as the primary endpoint as it is the gold standard to estimate portal venous pressure in trial participants with cirrhosis, i.e. assessing the severity of sinusoidal PH [R20-4090]. It is used as an established surrogate marker for improvement and / or worsening of liver fibrosis / function, since a decrease in HVPG translates into a clinically meaningful benefit [R20-1204]. The prognostic value of HVPG has been underlined by several landmark studies, showing that an HVPG ≥ 10 mmHg (i.e. CSPH) is predictive of the formation of varices [R20-4092], while a (pharmacologically-induced) decrease of HVPG modulates the respective risk of variceal growth and decompensation [R20-4093, R20-4091]. Hence, this also explains the choice of the secondary endpoint relating to the occurrence of further decompensation events (refer to Section 2.1.3). Other secondary endpoints (occurrence of significant hypotension or syncope, and occurrence of discontinuation due to hypotension or syncope) were chosen as they are relevant based on the mechanism of action of BI 685509.

Trial participants will be screened for the trial based on the eligibility criteria (refer to Sections 3.3.2 and 3.3.3). At Visit 1b (the final visit within the screening period) trial participants who remain eligible following Visits 1a will undergo their first HVPG measurement.

Non-invasive assessments (i.e. ultrasound and [redacted] have been chosen as part of the screening procedures to further investigate the trial participants' status, to establish baseline values for comparison with treatment, and to gain further insight into the use of non-invasive methods to investigate liver function and portal pressure. These assessments will be repeated (refer to Figure 3.1: 1 and the Flow Chart) to assess a time-dependency of the treatment.

Following randomisation, the trial design includes a dose-titration period. The mechanism related vasodilatation of BI 685509 can lead to orthostatic dysregulation and hypotensive episodes (refer to Table 1.4.2: 1). The orthostatic dysregulation is dose-limiting and clinical tolerability is improved if the dose is titrated. A BID administration also allows the total daily exposure of BI 685509 to be further increased while high peak concentrations are avoided. Hence, in this trial, a dose-titration regimen of [redacted] BID to [redacted] BID to [redacted] BID will be followed.

Trial participants selected for this trial have a risk for further decompensation. A DMC, independent from the Sponsor, will therefore be established to review safety data at intervals to identify any potential risks and / or the need for implementation of further safety measures. The tasks and responsibilities of the DMC members will be detailed in the DMC charter (refer to Section 8.7).

An independent AC will also be established for adjudication of hepatic injury. The tasks and responsibilities of the AC members will be detailed in the AC charter (refer to Section 8.7).

3.3 SELECTION OF TRIAL POPULATION

40 trial participants with CSPH in decompensated cirrhosis due to non-cholestatic liver disease will be randomized into the trial. Approximately 20 sites are planned across multiple countries. It is anticipated that 2 trial participants will be randomised at each site. If enrolment is delayed, additional sites may be recruited.

Screening of trial participants for this trial is competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of trial participants have been screened to deliver the required number of randomised trial participants. Investigators will be notified about the screening completion and will then not be allowed to screen additional trial participants for this trial. Trial participants already in screening at this time will be allowed to continue to randomisation if eligible.

Re-testing during the screening period is allowed once (e.g. if the Investigator believes an ineligible laboratory test is the result of an error or extenuating circumstances, the test can be repeated once without the trial participant having to be re-screened). Re-screening is also allowed once provided that the reasons for screen failure were reversible and have been resolved, based on Investigator judgement. A trial participant is considered a "re-screener" if

he / she was not eligible for the trial initially and is subsequently re-screened, going through the informed consent process for a second time, receiving a new unique trial participant number and repeating the screening period assessments.

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

If retrospectively it is found that a patient has been randomized in error (=did not meet all inclusion criteria or met one or more exclusion criteria), the sponsor or delegate should be contacted immediately. Based on an individual benefit-risk assessment a decision will be made whether continued trial participation is possible or not.

This trial will include an option for participants to complete anonymized questionnaires to provide feedback on their clinical trial experience. Providing this feedback is not required for trial participation, and information collected from these questionnaires will not be analysed as part of the clinical data for the trial (see Section 10.4)

3.3.1 Main diagnosis for trial entry

The trial will include trial participants with decompensated cirrhosis due to non-cholestatic liver disease after the first decompensation event, who are stabilized (CTP 5-7).

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial

2. Male or female who is ≥18 (or who is of legal age in countries where that is greater than 18) and ≤75 years old at screening (Visit 1a)

3. Diagnosis of cirrhosis due to non-cholestatic liver disease (including HCV, HBV, NASH, alcohol-related liver disease, autoimmune hepatitis, Wilson's disease, haemachromatosis, alpha-1 antitrypsin [A1At] deficiency)

4. One previous clinically significant decompensation event with clinical resolution at least 4 weeks prior start of screening (visit 1a):
   a. First variceal haemorrhage
   b. First episode of clinically significant ascites (requiring intervention in lifestyle [fluid and salt restriction] or medical treatment)

5. Willing and able to undergo HVPG measurements per protocol (based on Investigator judgement)

6. If receiving statins must be on a stable dose for at least 3 months prior to screening (Visit 1b), with no planned dose change throughout the trial

7. If receiving treatment with NSBBs or carvedilol must be on a stable dose for at least 1 month prior to screening (Visit 1b), with no planned dose change throughout the trial

8. For patient with alcohol-related cirrhosis, abstinence from significant alcohol misuse / abuse for a minimum of 2 months prior to screening (Visit 1a), and the ability to abstain from alcohol throughout the trial (both evaluated based on Investigator judgement)

9. WOCBP[1] must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly from the randomisation visit (Visit 2) until 7 days after the last treatment in this trial. The patient must agree to periodic pregnancy testing during participation in the trial. Refer to Section 4.2.2.3 and the patient information for a list of contraception methods meeting these criteria

10. Men able to father a child and who have a female sexual partner of CBP, must use a condom with or without spermicide, or adopt complete sexual abstinence, or be vasectomised (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate), from the randomisation visit (Visit 2) until 7 days after the last treatment in this trial. Refer to Section 4.2.2.3 and the patient information for further details

3.3.3 Exclusion criteria

1. History of cholestatic chronic liver disease (e.g. primary biliary cholangitis, primary sclerosing cholangitis)

2. Trial participants without adequate treatment for HBV, HCV or NASH as per local guidance (e.g. antiviral therapy for chronic HBV or HCV infection or lifestyle modification in NASH)

[1]A woman is considered of child-bearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Tubal ligation is NOT a method of permanent sterilisation. A post-menopausal state is defined as no menses for 12 months without an alternative medical cause.

3. If received curative anti-viral therapy for HCV, SVR sustained for less than 1 years prior to screening

4. If receiving anti-viral therapy for HBV, less than 6 months on a stable dose prior to screening, with planned dose change during the trial or HBV DNA detectable
5. Weight change ≥5% within 6 months prior screening in patients with NASH

6. Must take, or wishes to continue the intake of, restricted concomitant therapy (refer to Section 4.2.2.1) or any concomitant therapy considered likely (based on Investigator judgement) to interfere with the safe conduct of the trial

7. SBP <100 mmHg or DBP <70 mmHg at screening (Visit 1a)

8. Hepatic impairment defined as a Child-Turcotte-Pugh score ≥8 at screening

9. Model of End-stage Liver Disease (MELD) score of >15 at screening (Visit 1a), calculated by the central laboratory

10. ALT or AST >5 times upper limit of normal (ULN) at screening (Visit 1a), measured by the central laboratory

11. eGFR (CKD-EPI formula) < 20 mL/min/1.73 m^2 at screening (Visit 1a), measured by the central laboratory

12. Platelet count <50x10^9/L

13. Alpha-fetoprotein >50 ng/mL (>50 µg/L) at screening (Visit 1a), measured by the central laboratory

14. Prior orthotopic liver transplantation

15. Prior or planned TIPS or other porto-systemic bypass procedure during the trial conduct

16. Known portal vein thrombosis

17. History of clinically relevant orthostatic hypotension, fainting spells or blackouts due to hypotension or of unknown origin (based on Investigator judgement)

18. QTcF-interval >450 ms in men or >470 ms in women at screening (Visit 1a), a family history of long QT syndrome, or concomitant use of therapies with a known risk of Torsade de Pointes or planned initiation of such therapies during the trial (refer to Section 4.2.2.1)

19. Contraindication to any of the trial assessments (e.g. poor patient co-operation for HVPG, [redacted]

20. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to randomisation (Visit 2) or planned during the trial, e.g. hip replacement.

21. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening (Visit 1a), except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix

22. History of (in the 6 months prior to randomisation [Visit 2]), or ongoing, chronic drug abuse, or not expected to comply with the protocol requirements for any other reason that, based on Investigator judgement, makes the patient an unreliable trial recruit or unlikely to complete the trial as scheduled

23. Previous randomisation in this trial, previous exposure to BI 685509, or an allergy / contraindication to BI 685509 and matching placebo / or any of their excipients

24. Currently enrolled in another investigational device or drug trial, or less than 30 days or 5 half-lives (whichever is longer) prior to randomisation (Visit 2) since ending another investigational device or drug trial, or receiving other investigational treatment(s)

25. Women who are pregnant, nursing, or who plan to become pregnant while in the trial

26. Any other medical condition that, based on Investigator judgement, poses a safety risk for the patient or may interfere with the objectives of the trial

3.3.4 Discontinuation of trial participants from treatment or assessments

Trial participants 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.

However, if the trial participants agree, they should stay in the trial. Even if continued trial treatment is not possible, they should attend further trial visits to ensure their safety and to collect important trial data.

Measures to control the withdrawal rate include careful trial participant selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the trial participant files and CRF. If applicable, consider the requirements for AE collection reporting (see Section 5.2.6.2).

Trial participants who discontinue after randomisation will not be replaced and may not be re-enrolled later. However, the Sponsor may decide to randomise more trial participants than originally planned, to account for a reduced sample size, if trial participants terminate early due to e.g. trial disruption (such as measures to control a global pandemic).

3.3.4.1 Discontinuation of trial treatment

An individual trial participant will discontinue trial medication if:

- the trial participant wants to discontinue trial treatment. The trial participant will be asked to explain the reasons but has the right to refuse to answer.
- **the trial participant develops an AE:**
  - **CTCAE Grade 3 or higher and the AE was assessed by the Investigator as related to the trial treatment; OR**
  - **CTCAE grade 4 or higher regardless of attribution to the trial treatment**
- the trial participant has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both the investigator and sponsor representative, the safety of the trial participant cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future.
- the trial participant needs to take concomitant medication that interferes with the safety/efficacy of the investigational medicinal product or other trial treatment (refer to Section 4.2.2.1). If short-term, acute use of a restricted concomitant therapy is required (e.g. 5-7 days of antibiotic treatment for an infection), this will not automatically require discontinuation of BI 685509. Similarly, if a trial participant needs to modify a dose, where only a stable dose is permitted (e.g. NSBBs / carvedilol, statins, anti-viral therapy for HBV), this also will not automatically require discontinuation. In both cases, the Sponsor should be consulted.
- the trial participant meets the criteria for hepatic injury (refer to Section 5.2.6.1.4 and Appendix 10.2)
- the trial participant has an acute liver decompensation event such as VH, therapy-refractory ascites, overt encephalopathy, or other decompensation event based on Investigator judgement
- trial participants with worsening of their liver function (e.g. increase of Child Turcotte Pugh score of more than 2 points with clinical evidence of deteriorating liver function in the opinion of the Investigator). Refer to Child-Turcotte-Pugh classification method in Appendix 10.3
- trial participants with a QT or QTcF interval > 500 ms, or an increase of QT or QTcF of > 60 ms from the pre-dose value at Visit 2 / randomization (baseline). Such cases must be reported as AEs
- the trial participant can no longer receive trial medication for other medical reasons such as surgery, AEs, other diseases

- the trial participant´s treatment assignment has been unblended due to an emergency situation
- the trial participant has not successfully completed the dose titration period (i.e. Visit 4), but has persistent AEs or severe effects requiring down-titration of the trial medication (refer to Section 4.1.4.1)
- a female trial participant becomes pregnant. The trial participant will be followed up until birth or otherwise termination of the pregnancy. The data of the trial participant will be collected and reported in the Clinical Trial Report (CTR) until last trial participant last visit and any events thereafter will be reported in the BI Pharmacovigilance (PV) database (refer to Section 5.2.6.2.3)

Trial-specific procedures have also been defined for Investigators to follow in case of increased liver enzymes (AST, ALT, and total bilirubin) after randomisation. For details refer to Section 5.2.6.1.4 and Appendix 10.2 [P09-12413].

In the event of intolerance to BI 685509 after successful completion of the dose titration period at Visit 4 (e.g. persistent AEs despite two down-titrations, or severe effects at any dose), permanent treatment discontinuation should also be considered, based on Investigator judgement (refer to Section 4.1.4.1).

In addition to these criteria, the Investigator may discontinue trial participants at any time based on clinical judgement.

If a trial participant permanently discontinues the trial medication before the last allocated dose, an Early Discontinuation (ED) visit is required ideally within 7 days of discontinuing the medication. An EoS visit should be performed 2 weeks after the ED visit. Refer to Sections 6.2.2.1 and 6.2.3 for further details, including guidance with respect to trial assessments that should be included as part of an ED visit.

Boehringer Ingelheim will closely monitor and medically review all adverse events CTCAE Grade 3 and higher.

Boehringer Ingelheim will pause the enrollment of new patient in the trial and ensure the clinical data is reviewed by the data monitoring committee (DMC) for safety before proceeding with the trial if one of the following occurs:

1. more than two patients develop a CTCAE grade 3 or higher in the same category; OR
2. two or more patients meet the individual patient stopping criteria related to adverse event

In case of a temporary discontinuation, trial medication (BI 685509) should be restarted if medically justified; refer to Section 4.1.4 for details, including instructions regarding dose adjustments.

If new efficacy / safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all trial

participants or take any other appropriate actions to guarantee the safety of the trial participants.

3.3.4.2 Withdrawal of consent to trial participation

Trial participants may withdraw their consent to trial participation at any time without the need to justify the decision.

If a trial participant wants to withdraw consent, the investigator should be involved in the discussion with the trial participant 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.

If a patient withdraws consent for further trial participation, no further data will be collected from the respective patient.

Reporting of data of patients who discontinue/withdraw after randomization the active treatment phase is described in Section 7.2.1.

3.3.4.3 Discontinuation of the trial by the sponsor

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

- Failure to meet expected enrolment goals overall or at a particular trial site
- New efficacy or safety information invalidating the earlier positive benefit-risk assessment; please see Section 3.3.4.1.
- Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial
- Further treatment and follow up of trial participants affected will occur as described in Section 3.3.4.1.
- The investigator/the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational medicinal products in the trial is BI 685509 and placebo to match BI 685509. Boehringer Ingelheim will supply all products.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the investigational medicinal products are described in Tables 4.1.1: 1 to 4.1.1: 6 below.

Table 4.1.1: 1 BI 685509 [redacted]

Substance:	BI 685509
Pharmaceutical formulation:	Film-coated tablet
Unit strength:	[redacted]
Posology:	BID
Mode of administration:	Oral

Table 4.1.1: 2 BI 685509 [redacted]

Substance:	BI 685509
Pharmaceutical formulation:	Film-coated tablet
Unit strength:	[redacted]
Posology:	BID
Mode of administration:	Oral

Table 4.1.1: 3 BI 685509 [redacted]

Substance:	BI 685509
Pharmaceutical formulation:	Film-coated tablet
Unit strength:	[redacted]
Posology:	BID
Mode of administration:	Oral

Table 4.1.1: 4 Placebo to match BI 685509 [redacted]

Substance:	Placebo to match BI 685509 [redacted]
Pharmaceutical formulation:	Film-coated tablet
Unit strength:	Not applicable
Posology:	BID
Mode of administration:	Oral

Table 4.1.1: 5 Placebo to match BI 685509 [redacted]

Substance:	Placebo to match BI 685509 [redacted]
Pharmaceutical formulation:	Film-coated tablet
Unit strength:	Not applicable
Posology:	BID
Mode of administration:	Oral

Table 4.1.1: 6 Placebo to match BI 685509 [redacted]

Substance:	Placebo to match BI 685509 [redacted]
Pharmaceutical formulation:	Film-coated tablet
Unit strength:	Not applicable
Posology:	BID
Mode of administration:	Oral

4.1.2 Selection of doses in the trial and dose modifications

BI 685509 has been tested in a single rising dose trial, a food effect and DDI trial and two MRD trials in male healthy volunteers. Single doses ranged from [redacted] to [redacted] and multiple doses up to [redacted] daily were tested. Overall, BI 685509 was well tolerated except for dose-limiting orthostatic dysregulation. Up-titration and 3 times daily dosing markedly improved the cardiovascular tolerability (refer to the IB [c02778238]).

One phase 1 multiple oral rising dose trial and one phase 2 trial in trial participants with DN have also been completed. Multiple oral doses up to [redacted] TID were found to be safe and well tolerated. The highest total daily dose of [redacted] was achieved following up-titration in 2 steps over 14 days.

An estimated human dose of [redacted] mg BID is predicted to achieve pharmacologically relevant exposure in trial participants with hepatic impairment [c02778238, n00261471-01]. As [redacted] is the maximum tolerated single dose, 2 doses [redacted] BID and [redacted] BID) is being evaluated in the phase 2 trial 1366-0021 currently, that is conducted in trial participants with CSPH in compensated alcohol-related cirrhosis. These doses have been selected based on safety and PK results from the Phase I MRD hepatic impairment trial (1366-0020). In addition, [redacted] BI 685509 BID maintenance dose is also being evaluated in 3 trial participants groups (HBV, HCV and NASH) in trial 1366-0029.

In this trial, [redacted] BI 685509 BID maintenance dose will be evaluated in trial participants with CSPH in decompensated cirrhosis due to non-cholestatic liver diseases, with the potential to down-titrate, if not tolerated just as in trials 1366-0021 and 1366-0029

4.1.3 Method of assigning trial participants to treatment groups

After the assessment of all in- and exclusion criteria, each eligible trial participant will be randomised in a blinded fashion to treatment groups according to a randomisation plan in a

1:1 ratio at Visit 2 via an Interactive Response Technology (IRT) system. Refer to Section 7.4 for further details regarding randomisation and access to the randomisation code.

Note that the medication numbers, assigned via the IRT system at each dispensing visit, are different from the trial participant number (which is generated via the IRT system when a new trial participant is registered [screened] in the system).

The Investigator (and relevant designated site personnel) will be provided with instructions to access the IRT system.

4.1.4 Drug assignment and administration of doses for each trial participant

Trial medication will be dispensed at the investigational sites in accordance with the Flow Chart. At dispensing visits trial participants will be given the appropriate number of medication kits for BI 685509 (range 1-2) depending on the interval between the visits (for further kit details refer to Section 4.1.6). The last dose of BI 685509 will be administered in the evening of the day before the EoT visit.

All trial participants, regardless of the treatment group they are assigned to, will start at Visit 2 on a dose of [redacted] BI 685509 BID or matching placebo. At Visit 3, 7 days later, and again at Visit 4, a further 7 days after Visit 3, all trial participants will be up-titrated first to a dose of [redacted] BI 685509 BID or matching placebo, and then to a dose of [redacted] BI 685509 BID or matching placebo. In this way the blind across treatment groups will be maintained (refer to Table 4.1.4: 1). Trial participants will be informed about the dose titration period and will be made aware that up-titration for BI 685509 is being used. If a trial participant does not tolerate an up-titration, e.g. due to orthostatic dysregulation, the rules in Section 4.1.4.1 must be followed. From Visit 4 onwards, trial participants will continue to receive the maximum dose of 3mg BI 685509 BID (unless a down-titration is required), until reaching the EoT visit 8 weeks after starting the trial medication.

If a trial participant has an AE that, based on Investigator judgement, may be related to BI 685509, the trial medication can either be:

- interrupted (i.e. the trial medication is stopped, and subsequently re-started. The up-titration approach described above is followed.)

OR

- the dose can be reduced (down-titrated) for BI 685509 if the trial participant has successfully completed the dose titration period (i.e. Visit 4).

For further details refer to Sections 4.1.4.1 and 4.1.4.2.

All trial medication assignments, including up / down-titrations for BI 685509 and provision of replacement kits, will be managed through the IRT system. Down-titrations of BI 685509 must not be performed by instructing the trial participant to take less than the two daily doses (refer to Section 4.1.4.1).

Table 4.1.4: 1 Drug assignment and dosage by treatment group

Randomisation Allocation	**Week 1 of Treatment**	**Week 2 of Treatment**	**Week 3 of Treatment Onwards**
	Dispensed at Visit 2	**Dispensed at Visit 3**	**Dispensed at Visit 4 onwards**
Treatment group 1 (BI 685509 [redacted] *BID*)	[redacted] **BI 685509**	[redacted] **BI 685509 (Up-titration)**	[redacted] **BI 685509 (Up-titration)**
Treatment group 2 (Placebo to BI 685509)	[redacted] **BI 685509 matching placebo**	[redacted] **BI 685509 matching placebo (Up-titration)**	[redacted] **BI 685509 matching placebo (Up-titration)**

From the start of the treatment period (i.e. from Visit 2), and until reaching the EoT visit 8 weeks later, trial participants will be instructed to take BI 685509 orally twice a day (BID). Each dose of BI 685509 will consist of one film-coated tablet. It is recommended that the first daily dose is taken in the morning, and the second dose in the evening. Ideally there should be at least 10 hours in between the intake of each dose. BI 685509 should be taken at approximately the same time every day. If a dose is missed this must not be rectified by taking two doses (i.e. double doses) at the next time point; if a dose is missed by more than 6 hours, that dose should be skipped altogether and the next dose taken as scheduled. Also refer to Section 4.1.4.2 for further details regarding interruption of trial medication. Trial medication should be taken with a glass of water and can be taken with or without food.
In the morning of a visit, the trial medication will be administered as part of the visit. Therefore, on these days, trial participants should be instructed not to take their morning dose in advance of the visits. [redacted] Trial participants who fail to follow these instructions should have the visit re-scheduled as soon as possible, ideally on the following day (refer to Section 6.1). On days with no scheduled visit the trial participant will self-administer their medication at home. Trial participants should be instructed to bring all unused trial medication and empty wallets / packaging with them when they return for clinic visits to the investigational site.

[redacted]

In case of a temporary interruption to treatment, refer to Sections 3.3.4.1, 4.1.4.1 and 4.1.4.2. In the event of force majeure or other disrupting circumstances (e.g. pandemic, war; refer to Section 6) physical trial participant visits to sites may not be feasible or may need to be restricted to ensure trial participant safety. Based on a thorough assessment of the benefits and risks, the Investigator may still decide to continue trial medication, and, if acceptable according to local law and regulations, trial medication may be shipped from the site to the trial participant's home.

4.1.4.1 Rules for down-titration in case of intolerance to BI 685509

If a trial participant has an AE that, based on Investigator judgement, may be related to trial medication, the down-titration rules below must be followed. These rules apply if the trial participant has successfully completed the dose titration period (i.e. Visit 4) and is either still taking their final assigned dose of trial medication, or if they have missed ≤3 consecutive doses[1]. If the trial participant has not successfully completed the dose titration period (i.e. Visit 4), down-titration is not permitted; in case of persistent AEs or severe effects, the trial participant must permanently discontinue treatment (refer to Section 3.3.4.1).

- if the trial participant is receiving [redacted] BID BI 685509 the dose will be down-titrated one level to 2 mg BID BI 685509

Once down-titration has taken place, no further up-titration will be permitted.
If a trial participant continues to have an AE, or a new AE develops, that based on Investigator judgement, may be related to trial medication, a second down-titration will be permitted:

- if the trial participant is receiving [redacted] BID BI 685509 the dose will be down-titrated to [redacted] BID BI 685509

Down-titration must not be performed by taking less than the two daily doses or by splitting tablets so that a whole tablet is not taken. Down-titration will be managed through the IRT system (refer to Section 4.1.4). After the successful completion of the dose titration period (i.e. Visit 4), in case of persistent AEs despite down-titration, or severe effects at any dose, permanent treatment discontinuation should be considered (refer to Section 3.3.4.1). Trial participants who are down-titrated will need to return to the investigational site to receive their continuing supply of trial medication, either at the next scheduled visit or via an unscheduled visit.

4.1.4.2 Rules for re-starting up-titration in case of interruption of BI 685509

An interruption of BI 685509 may have an influence on the tolerability. Hence, if a trial participant has missed > 3 consecutive doses[1] of trial medication for any reason (e.g. due to an AE, or for compliance reasons), the rules below will apply for the safety of the trial participant. If ≤ 3 consecutive doses of trial medication have been missed and there is no related AE, then the next dose of trial medication should be taken as scheduled.

- after an interruption of trial medication of >3 consecutive doses, the trial participant should re-start the dose titration period at [redacted] BID BI 685509 / matching placebo
- before any further up-titration occurs the trial participant must have taken the preceding dose for at least 7 consecutive days. This applies throughout the treatment period
  - this may mean that a trial participant due to be up-titrated at Visit 3 or 4 (as per Table 4.1.4: 1) is held at their current dose until their next scheduled visit. They could also be up-titrated at an unscheduled visit once this requirement is met
- if interruption occurs after Visit 4, subsequent up-titration will be allowed either at a scheduled visit or at an unscheduled visit

Trial participants with an interruption of trial medication will need to return to the investigational site to receive their continuing supply of trial medication, either at the next scheduled visit or via an unscheduled visit.

[1] Footnote: One dose refers to an individual time point e.g. morning dose or evening dose.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Trial participants, investigators, central reviewers, and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded regarding the randomised treatment assignments until the database is declared ready for analysis according to the sponsor's SOPs. Further details regarding the timepoint of unblinding the database for analysis are documented in the TSAP.

The access to the randomisation code will be kept restricted until its documented release per sponsor SOP.

The randomisation codes will be provided to bioanalytics before the last trial participant completes the trial to allow for the [redacted] Bioanalytics will not disclose the randomisation code or the results of their measurements until the trial is officially unblinded after the database lock (DBL).

[redacted] specific data must be unblinded and the treatment information must be made available to selected individuals (e.g. [redacted]). The unblinding procedure and logistics specific to this purpose will be provided in a separate document. It should be noted [redacted] will be communicated to the project and trial team prior to DBL.

A DMC, independent from the Sponsor, will perform an unblinded safety evaluation at intervals specified in the DMC charter in order to ensure that trial participants are protected from potential harm (refer to Section 8.7). A trial independent statistician (iSTAT) will be assigned to prepare tables and listings as well as the summary reports for the DMC based on the agreed upon format and layout. Randomisation codes will be provided to the iSTAT. All information, including AEs, mortality, laboratory parameters, and decisions from hepatic injury adjudication will be provided in an unblinded fashion. This will be accomplished by using coded labels and by providing the DMC members with the decoding information separately, if needed.

4.1.5.2 Emergency unblinding and breaking the code

Emergency unblinding will be available to the Investigator via IRT. It must only be used in an emergency situation when the identity of the trial medication must be known to the Investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and / or appropriate eCRF page. If a trial participant is unblinded by the Investigator, the trial participant has to be discontinued from the trial (refer to Section 3.3.4.1).

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's PV group to access the randomisation code for individual trial participants during trial conduct. The access to the

code will only be given to authorised PV representatives for processing in the PV database system and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by Boehringer Ingelheim or a designated Clinical Research Organisation (CRO). They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice. Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

In this trial, each medication kit with BID BI 685509 will contain one wallet and each wallet will hold 20 film-coated tablets (i.e. seven days treatment plus three days reserve). The number of kits dispensed at each dispensing visit, will be sufficient to cover both the planned number of weeks of treatment between visits, and the use of any permitted visit windows.

For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the Clinical Research Associate (CRA), as provided in the list of contacts in the ISF, must be contacted immediately.

4.1.8 Drug accountability

The Investigator or designee will receive the trial medication delivered by the Sponsor or delegate when the following requirements are fulfilled:

- approval of the CTP by the Institutional Review Board (IRB) / Independent Ethics Committee (IEC)
- availability of a signed and dated clinical trial contract between the Sponsor or delegate and the investigational site
- approval / notification of the regulatory authority, e.g. competent authority (CA)
- availability of the curriculum vitae of the Principal Investigator
- availability of a signed and dated CTP
- availability of the proof of a medical license for the Principal Investigator (if applicable)
- availability of FDA Form 1572 (if applicable)

Trial medication is not allowed to be used outside the context of this CTP. It must not be forwarded to other Investigators or clinics. Trial participants should be instructed to return unused trial medication.

The Investigator or designee must maintain records of the medication's delivery to the trial site, the inventory at the site, the use by each trial participant, and the return to the Sponsor or warehouse / drug distribution center or alternative disposal of unused medication. If applicable, the Sponsor or warehouse / drug distribution center will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the trial medication and trial participants. The Investigator or designee will maintain records that document adequately that the trial participants were provided the doses specified by the CTP and reconcile all trial medication received from the Sponsor. At the time of return to the Sponsor and / or appointed CRO, the Investigator or designee must verify that all unused or partially used trial medication has been returned by the clinical trial participant and that no remaining supplies are in the Investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed.

Stable doses of concomitant therapies for chronic conditions, for which neither the condition nor the treatment are judged to exclude the trial participant from participation (refer to Section 3.3) are permissible throughout the duration of the trial. Refer to Section 4.2.2.1 for restrictions with respect to statins, NSBBs / carvedilol and anti-viral treatment for HBV. All concomitant therapy should be carefully evaluated by the Investigator and the Sponsor should be contacted when there are questions.

In case of AEs in need of treatment, any concomitant therapy, based on Investigator's judgement, will be permitted. Diagnostics and treatment should be initiated according to local standard of care.

All concomitant therapies will be recorded on the appropriate pages of the eCRF.

Endoscopic variceal ligation (performed according to local guidelines) is permitted during the trial as required. The procedure should be recorded on the appropriate page of the eCRF.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The concomitant therapies mentioned below must not be co-administered with BI 685509 (also refer to Table 1.4.2: 1).

- NO-sGC-cGMP pathway activating therapies like NO-donors (e.g. glyceryl trinitrate, isosorbide di- or mono-nitrate, molsidomine), PDE-5-inhibitors (e.g. sildenafil,

tadalafil, and vardenafil), non-specific PDE inhibitors such as dipyridamole and theophylline, or sGC-stimulators (e.g. riociguat): These restrictions apply from within 5 half-lives after the concomitant therapy has been stopped prior to enrolment (visit 2), until the EoS visit.

- Concomitant therapies with a known risk of Torsade de Pointes: These restrictions apply from screening Visit 1a, until the EoS visit. In the event of temporary concomitant use of such a therapy, the trial medication must be temporarily stopped and can then be re-started at least 5 half-lives after the concomitant therapy with the known risk of Torsade de Pointes has been stopped. Refer to Section 4.1.4.2 for rules for re-starting up-titration in case of interruption of trial medication.

- clinically relevant OATP1B1/3 inhibitors

- clinically relevant concomitant therapies known to inhibit or induce UGT enzymes

In the event of temporary concomitant use of medication that is not permitted, BI 685509 must be temporarily stopped and can be re-started after a period of at least 5 half-lives after the concomitant therapy has been stopped. Refer to Section 4.1.4.2 for rules for re-starting up-titration in case of interruption of BI 685509.

A list to support the identification of the above-mentioned concomitant therapies will be provided in the ISF. The list will not claim completeness.

Furthermore, trial participants who are receiving statins, must be on a stable dose for at least 3 months prior to screening (Visit 1b), with no planned dose change throughout the trial, and trial participants who are receiving NSBBs / carvedilol, must be on a stable dose for at least 1 month prior to screening (Visit 1b), with no planned dose change throughout the trial (refer to Section 3.3.2). In addition, these concomitant therapies should not be initiated during the trial as they will interfere with the efficacy of the trial medication (refer to Section 3.3.4.1).

If receiving anti-viral therapy for HBV, trial participants must be on a stable dose for at least 6 months prior to screening, with no planned dose change throughout the trial.

4.2.2.1.1 Close monitoring for AEs based on concomitant therapy

If a trial participant is taking concomitant therapy that is metabolised by CYP3A4 and/or CYP2C8, which has a narrow therapeutic index and / or is a sensitive substrate, close monitoring for AEs is recommended in this trial (also refer to Table 1.4.2: 1). A list to support the identification of the above-mentioned concomitant therapies will also be provided in the ISF. The list will not claim completeness.

4.2.2.2 Restrictions on diet and lifestyle

Drastic changes of diet and lifestyle in the course of the trial should be avoided. This includes unusual and strenuous exercise for the trial participant (e.g. taking up exercises that put pressure on the abdomen, such as weightlifting).
Alcohol consumption should be avoided throughout the trial; excessive alcohol consumption could lead to hypotension when taken concomitantly with BI 685509.
During the treatment period, trial participants will be asked if they have consumed any alcohol, and where necessary, reminders should be issued to abstain from alcohol consumption.

The requirement for a fasting status upon arrival at clinic visits is as defined in the Flow Chart. Once all visit assessments are complete that require this status, the trial participant may eat as normal.

4.2.2.3 Contraception requirements

Women of childbearing potential (WOCBP) and men able to father a child must use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the trial participant information.

WOCBP (for the definition refer to Section 3.3.2) must be ready and able to use a highly effective method of birth control from the randomisation visit (Visit 2) until 7 days after the last trial medication intake, if their partner is a male able to father a child. No contraceptive is required for the partner of the WOCBP.

Highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly include (if local regulations permit):

- combined (oestrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal)
- progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable)
- intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion

A male trial participant must use a condom with or without spermicide until at least 7 days after last trial medication intake if their sexual partner is a WOCBP, or, be vasectomised with documented absence of sperm in the ejaculate. No contraceptive is required for the male trial participant's partner.

Alternatively, WOCBP and male trial participants able to father a child must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the trial participant. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods; declaration of abstinence for the duration of exposure to trial medication; and withdrawal are not acceptable.

4.3 TREATMENT COMPLIANCE

Trial participants are requested to bring all remaining trial medication including empty package material with them when attending visits.
Based on tablet counts, treatment compliance will be calculated as shown in the formula below. Compliance will be verified by the CRA authorised by the sponsor or delegate.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of actually taken} \times 100}{\text{Number of which should have been taken as directed by the investigator}}$$

If the number of doses taken is not between 80-120%, site staff will explain to the trial participant the importance of treatment compliance.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Hepatic venous pressure gradient

HVPG measurement will be performed at the time points specified in the Flow Chart. Sites must have access to the necessary infrastructure and equipment to measure HVPG (e.g. a hepatic hemodynamic laboratory at their site, or at a nearby institution). Site staff performing the procedure must have sufficient expertise (e.g. performing in the region of 25 or more HVPG measurements per year) with interventional skills and expertise in the reading of pressure tracings, since a local interpretation of the tracing from Visit 1b and EoT visit will be recorded in the trial participant source documents and the eCRF.

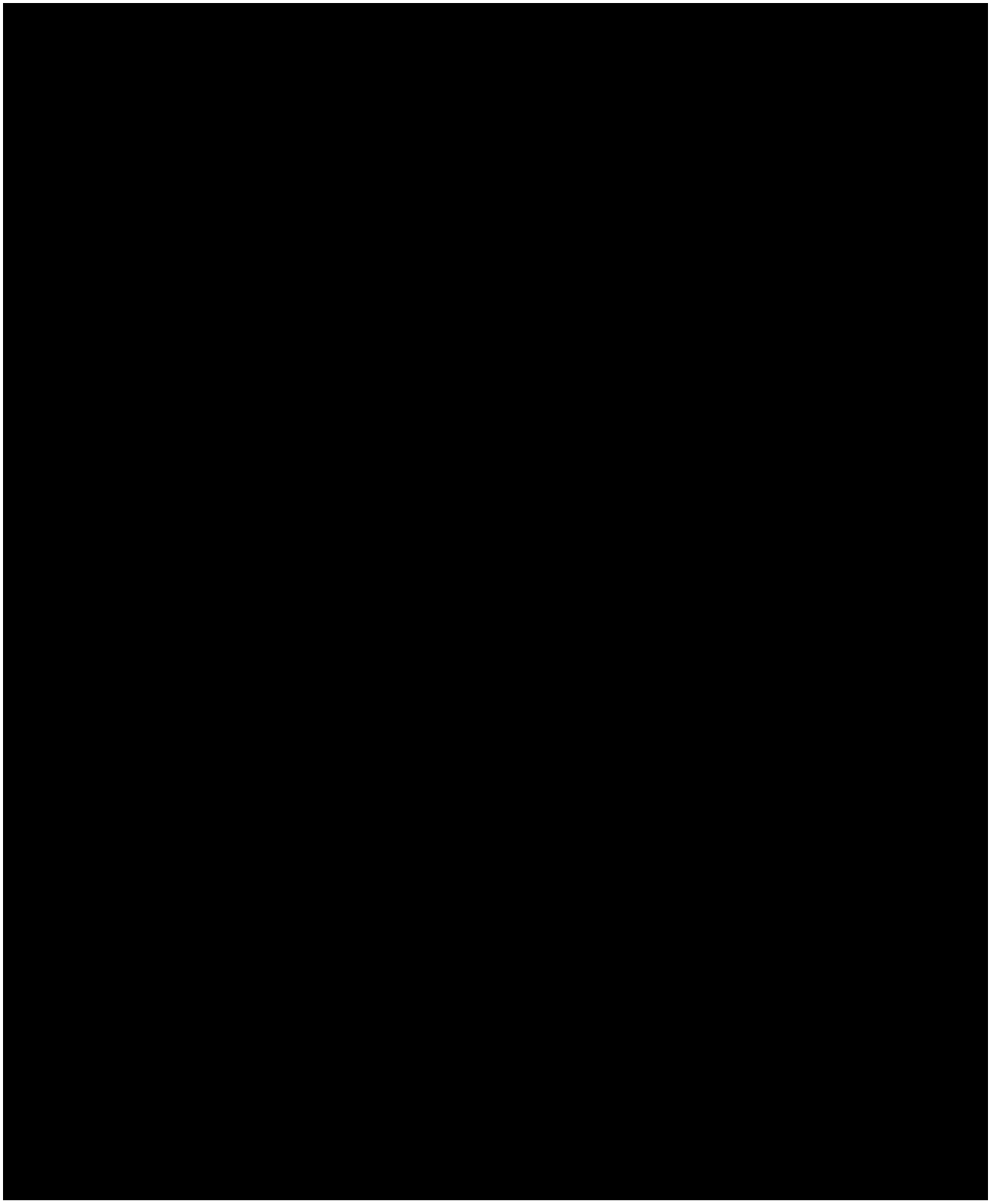
The HVPG procedure within the trial will be conducted in a standardised fashion at all sites (for details refer to the HVPG manual in the ISF); training will be provided. Each trial site will be asked to provide acceptable sample HVPG tracing(s) prior to commencing trial participant recruitment if not already provided for Trials 1366-0021 or 1366-0029. Measurements of wedged hepatic venous pressure (WHVP) and free hepatic venous pressure (FHVP) will be performed in triplicate; tracings will be provided to an external Supplier and read centrally by independent expert(s) in PH; the central read will include a subjective assessment of the overall trace quality as well as a read of the relevant pressures. The independent expert(s) will be blinded to the timepoint that the trace relates to. The central read will include the traces from Visit 1b that have also been interpreted locally. The results of the central read will be transferred to the Sponsor and will be considered the official evaluation of the trial. In case of discrepancies between a local interpretation and the central evaluation (e.g. of the Visit 1b tracing), the central evaluation will remain valid.

HVPG measurements should be performed using the same hepatic vein, prior to intake of the trial medication, after an overnight fast, and ideally in the morning. If it is not possible to perform the measurement at Visit 1b in the morning an alternative time of day can be chosen; in this case, a fast of at least four hours is required. The subsequent HVPG measurement must then be performed at approximately the same time of day as the Visit 1b measurement for a single trial participant.

At the EoT visit, the HVPG measurement should be performed on the day of the scheduled visit, or within seven days (if this latter approach is taken, the measurement should still be performed after an overnight fast / after a fast of at least four hours). If this scenario is chosen for an HVPG performed during the treatment period, the morning dose of trial medication can be taken prior to the procedure. In the event of early discontinuation from the trial, refer to Section 6.2.2.1 for guidance regarding the HVPG measurement at the ED visit.

A summary of the HVPG procedure is as follows [R20-3977]:
Under local anaesthesia and ultrasound guidance, a catheter introducer sheath is placed in the right internal jugular vein. Using fluoroscopic guidance, a balloon catheter is advanced into the inferior vena cava (IVC) and inserted into a large hepatic vein. Correct and sufficient wedge position of the catheter is ensured by injecting contrast media while the balloon is blocking the outflow of the cannulated hepatic vein. After calibrating the external pressure

transducer, continuous pressure recordings are obtained with triplicate recordings of the WHVP and FHVP. The difference between FHVP and WHVP is referred to as HVPG, with values ≥ 10 mmHg indicating CSPH. Before removing the catheter, pressure readings obtained in the IVC at the same level, as well as the right atrial pressure, are recorded.



[redacted]

5.2.1 Physical examination

A complete physical examination must be performed at the two time points specified in the Flow Chart; further physical examinations are only required if the trial participant reports symptoms. A complete physical examination includes, as a minimum, general appearance, neck, lungs, cardiovascular system, abdomen, extremities and skin.

5.2.1.1 Anthropometric measurements (height, weight, waist and hip circumference)

Measurement of height, body weight, waist and hip circumference will be performed at the time points specified in the Flow Chart. Height will be measured at Visit 1a only. The results of anthropometric measurements must be included in the source documents available at the site.

Whenever possible, weight measurements should always be performed on the same weighing scales for one trial participant. In order to get comparable body weight values, the assessment should be performed in the following way:

- shoes, coat / jackets and any headgear should be taken off
- pockets should be emptied of heavy objects (i.e. keys, coins etc)
- after bladder voiding

The measuring tape used for waist and hip circumference should be made of a material that is not easily stretched, such as fiberglass. Waist circumference measurements should be made around a trial participant's bare midriff, after the trial participant exhales while standing without shoes and with both feet touching and arms hanging freely. Waist circumference should be determined by measuring the midpoint between the lowest rib and the iliac crest. The tape should be placed perpendicular to the long axis of the body and horizontal to the floor and applied with sufficient tension to conform to the measurement surface.

Hip circumference measurements should start at one hip, wrapping the measuring tape around the widest part of the buttocks, and around the other hip to the front. Coats / jackets should be taken off and pockets emptied to ensure a close measurement and with both feet touching and arms hanging freely.

5.2.2 Vital signs / home blood pressure and heart rate monitoring

Vital signs (SBP, DBP, as well as HR [pulse rate]) will be evaluated at trial visits at the time points specified in the Flow Chart, prior to blood sampling and prior to the 12-lead ECG. BP measurements should be recorded in the eCRF to the nearest 1 mmHg. BP measurements should be performed on the non-dominant arm. HR should be measured electronically or by palpation, and counted for one minute. BP and HR measurements should be taken after trial participants have rested quietly, in the seated / supine position, for at least 5 minutes. The measurements recorded at the trial visit must be included in the source documents available at the site.

At screening (Visit 1a), the site should use their preferred method to measure vital signs. From Visit 2 onwards, vital signs should be measured using the trial participants home BP monitoring equipment (refer to Section 5.2.2.1) in order to have a consistent method for the duration of the trial. This includes the pre- and post-dose vital signs measurements during the dose-titration period and at the subsequent visit (refer to the Flow Chart and Section 6.2).

5.2.2.1 Home blood pressure and heart rate monitoring

Home BP and HR monitoring will be performed by the trial participant as specified in the Flow Chart. Electronic BP and HR monitoring equipment will be provided for this purpose. Site staff will train the trial participant in the correct use of the equipment at Visit 2, explaining that it must be used only to record BP and HR measurements belonging to the trial participant. Subsequent refresher training should be provided at subsequent visits if required.

Trial participants will be asked to measure their BP and HR every day in the morning, soon after waking up prior to much physical activity, and after resting seated for approximately 5 minutes. Measurements must be taken before administration of the morning dose of trial medication. The electronic readings will be stored in the memory of the home BP and HR monitoring equipment.

If, at any time after trial medication intake, a trial participant experiences symptoms suggestive of hypotension (e.g. he / she feels light-headed / dizzy, sees black spots, suffers from weakness etc.), particularly if the symptoms occur whilst standing up, or if he / she has any other symptoms in between trial visits, additional BP and HR reading(s) can be taken and the trial participant should report these symptoms at the next trial visit. The trial participant should bring the home BP and HR monitoring equipment with them to each trial visit (refer to the Flow Chart) for the site staff to review the electronic readings, and to use for the measurement of BP and HR during trial visits from Visit 2 onwards (refer to Section 5.2.2). Any BP / HR measurements which, following review, are evaluated as AEs, must be included in the source documents available at the site (refer to Section 8.3.1).

5.2.3 Safety laboratory parameters

Safety laboratory parameters that will be assessed are listed in Table 5.2.3: 1. Sampling time points will be as indicated in the Flow Chart. All analyses will be performed by a central laboratory; the respective reference ranges will be provided in the ISF. Refer to Table 5.2.3:2 for a list of "minimum required safety laboratory parameters" in the event of force majeure or other disruptive circumstances.

Trial participants should be fasted for blood sampling for the safety laboratory where that visit is defined as a fasting visit in the Flow Chart; where a non-fasting status is defined, the safety laboratory sample can be collected in a non-fasting status. [redacted] Blood samples for safety laboratory parameters should be drawn prior to administration of trial medication.

Instructions regarding sample collection, sample handling / processing and sample shipping will be provided in the central laboratory manual in the ISF.

The central laboratory will provide laboratory reports to the Investigator. It is the responsibility of the Investigator to evaluate these reports. Clinically relevant abnormal findings, as judged by the Investigator, must be reported as AEs (refer to Section 5.2.6).

Laboratory tests may need to be repeated in case of required medical follow-up due to an AE or if a test was not successful due to incorrect specimen handling or storage. Should a trial participant not fulfil all laboratory requirements to take part in the trial due to a transitional medical condition, the trial participant may continue in the screening period but cannot be randomised until the re-test of the laboratory result is available to determine the eligibility of the trial participant (refer to Section 3.3).

In case that the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (refer to Section 5.2.6.1.4 for the DILI checklist which can be downloaded from the electronic data capture [eDC] system, and Appendix 10.2). The amount of blood taken from the trial participant concerned will be increased due to this additional sampling.

The CKD-EPI formula (isotope dilution mass spectrometry standardised) will be used for reporting eGFR based on serum creatinine.

The central laboratory will transfer the results of the analysis to the Sponsor or delegate.

In case that the qualitative parameters are abnormal, a quantitative analysis will be performed by the central laboratory.

Table 5.2.3: 1 Safety laboratory tests

Category	**Test name**	**Short Name (BI Laboratory Test Code, LBSPID)**
Haematology	WBC count / leukocytes	WBC
	Platelet count / thrombocytes	PLTCT
	Reticulocytes	RETABS
	Haemoglobin	HGB
	RBC count / erythrocytes	RBC
Automatic WBC differential (absolute and percentage)	Neutrophils	SEGABS
	Eosinophils	EOSABS
	Basophils	BASABS
	Monocytes	MONABS
	Lymphocytes	LYMABS

Table 5.2.3: 1 (cont.) Safety laboratory tests

Category	Test name	Short Name (BI Laboratory Test Code, LBSPID)
Coagulation	aPTT	APTTS
	PT	PRTSEC
	INR	INR
	Fibrinogen	FIBR
Clinical chemistry	ALT	SGPT
	Alpha fetoprotein[4]	AFP
	Albumin	ALB
	Alkaline phosphatase	ALKP
	AST	SGOT
	Bilirubin (total)	TBILI
	Bilirubin (direct)	BILID
	Bilirubin (indirect)	BILII
	hs-CRP	CRPHS
	Creatinine, serum	CRE
	CK	CK
	CK-MB[1]	CKMBABS
	eGFR	GFRE
	ɣ-GT	GGT
	Glucose	GLUB
	LDH	LDH
	Lipase	LIPASE
	Phosphatidylethanol (PEth)[2]	PETH
	Protein (total)	TPRO
	Troponin I[1]	TPONI
	Urea (BUN)	UREA
	Uric acid	URIC
	Brain Natriuretic Peptide (BNP)	BNP

Table 5.2.3: 1 (cont.) Safety laboratory tests

Category	Test name	Short Name (BI Laboratory Test Code, LBSPID)
Electrolytes	Bicarbonate	BICARB
	Calcium	CA
	Chloride	CL
	Magnesium	MG
	Phosphate	P
	Potassium	K
	Sodium	NA
Lipids[4]	HDL	HDL
	LDL	LDL
	Cholesterol (total)	CHOL
	Triglycerides	TRIGL
Hormones	TSH[4]	TSH
	Free T3[5]	FT3
	Free T4[5]	FT4V
Pregnancy test (serum)	Human Chorionic Gonadotropin[6]	HCG
Pregnancy test (urine)	Human Chorionic Gonadotropin[7]	Not Applicable
Infections screening[4]	HCV antibody (qualitative)	HCAB
	HCV RNA PCR[8]	HCVRNA
	HBV surface antigen (qualitative)	HBSAG
	HBV core antibody (qualitative)	HBCAB
	HBV – DNA[9]	HBVDNAV
Urine chemistry	Urine albumin	UALBUM
Urinalysis (semi-quantitative)	Urine nitrite	UNIT
	Urine protein	UPROZ
	Urine glucose	UGLU
	Urine ketone	UKET
	Urobilinogen	UROBZ
	Urine bilirubin	UBILI
	Urine blood	UHGB
	Urine leukocyte esterase	ULEUKES
	Urine pH	UPH

1. If initial CK is elevated, re-test CK with CK-MB and troponin I
2. Not performed at screening (Visit 1a). PEth, an alcohol-specific biomarker, will be measured during the treatment period for data analysis purposes
3. Not performed at screening (Visit 1a);
4. Only performed at screening (Visit 1a)

5. Reflex in case of abnormal TSH
6. WOCBP only; only at Visit 1a, and as a reflex if urine testing is positive
7. WOCBP only, Visit 2 onwards. Measured locally at the site every 4 weeks using a pregnancy test kit provided by the central laboratory. Serum pregnancy testing will be done as a reflex if urine testing is positive (see above). More frequent pregnancy testing should be done if required by local regulation and /or authority or per investigator judgement. Pregnancy testing at dosing visits should be completed prior to administration of the trial medication
8. Reflex in case of positive HCV antibody
9. Reflex in case of positive HBV core antibody

Table 5.2.3: 2 Minimum required safety laboratory tests (force majeure / other disruptive circumstances)

Category	Test name	Short Name (BI Laboratory Test Code, LBSPID)
Haematology	Haemoglobin	HGB
	RBC count / erythrocytes	RBC
	WBC count / leukocytes	WBC
	Platelet count / thrombocytes	PLTCT
Clinical chemistry	ALT	SGPT
	Albumin	ALB
	Alkaline phosphatase	ALKP
	AST	SGOT
	Bilirubin (total)	TBILI
	Creatinine	CRE
	Potassium	K
	Sodium	NA

5.2.4 Electrocardiogram

The 12-lead ECGs will be recorded at the time points specified in the Flow Chart; the ECGs should be performed prior to blood sampling and intake of trial medication [redacted]

During the dose-titration period (i.e. when up-titration is occurring) and at the subsequent visit, 12-lead ECGs will also be performed approximately 1 hour and 2 hours after intake of trial medication. These ECGs should precede the 1 hour and 2 hour [redacted] (refer to Section 5.3.1).

ECGs must be administered by a qualified physician, nurse or technologist. The Investigator or delegate will evaluate whether the ECG is normal or abnormal and assess clinical relevance. An ECG may be repeated for quality reasons and the repeated recording used for analysis. If necessary, additional ECGs may be recorded for safety reasons.

Dated and signed print-outs of the ECG, with findings, should be documented in the trial participant's medical record. Clinically relevant abnormal findings will be reported either as a baseline condition (if identified at the screening visit [Visit 1a]) or otherwise as AEs and will be followed up and / or treated as medically appropriate. ECG abnormalities will be carefully assessed by the Investigator or delegate, and if trial discontinuation criteria are met (refer to Section 3.3.4.1), the trial participant will be discontinued from the trial.

Copies of ECGs will be sent to a central ECG Supplier for storage purposes. This will enable a subsequent centralised and independent re-evaluation if necessary.

5.2.5 Other safety parameters

5.2.5.1 Ultrasound (liver and spleen)

Ultrasound imaging of the liver and spleen will be performed after an overnight fast, using local site equipment, and at the time points specified in the Flow Chart. [redacted]

During the treatment period, following randomisation, ultrasound assessments should be performed on the day of the scheduled visit, or within seven days (if this latter approach is taken, the assessment must still be performed after an overnight fast). In the event of early discontinuation from the trial, refer to Section 6.2.2.1 for guidance regarding testing at the ED visit.

Ultrasound is used as a safety measure to assess the condition of the liver and spleen, organ size and the presence of ascites. The skin-to-liver capsule distance (i.e. the subcutaneous thickness), portal vein diameter, the skin-to-spleen capsule distance, and spleen height, length and width will also be measured, since large distances can affect the ability to sufficiently measure [redacted]

Sites will be expected to follow local standard processes prior to and during the procedure.

5.2.5.2 Hepatic injury adjudication

An independent AC will be used to adjudicate certain hepatic events for severity and causal relationship with the trial medication. For further details refer to Section 8.7.

5.2.6 Assessment of adverse events

Data and information necessary for the thorough assessment of AEs, SAEs, and AESIs will be reported to the sponsor via eCRF. This may include specific data and information not prospectively specified in this protocol.

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a trial participant 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 considered related or not.

The following should also be recorded as an appropriate eCRF :

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

5.2.6.1.2 Serious adverse event

A 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 trial participant 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 intrial participant hospitalisation or 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 on appropriate medical judgement which may jeopardise the trial participant and may require medial 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.

For Japan only: An event that possibly leads to disability will be handled as ‘deemed serious for any other reason’ and, therefore, reported as an SAE.

5.2.6.1.3 AEs considered “Always Serious”

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of 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. A copy of the latest list of “Always Serious AEs” will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2. Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in Section 5.2.6.2, subsections “AE Collection” and “AE reporting to sponsor and timelines”.

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:

- Hepatic injury
  A hepatic injury is defined by alterations of the hepatic laboratory and clinical parameters after randomisation as detailed by the removal and stopping criteria in Section 3.3.4.1 and Appendix 10.2

  These laboratory findings constitute a hepatic injury alert and patients showing these abnormalities need to be followed up according to the "DILI checklist" which can be downloaded from the eDC system. In case of clinical symptoms of hepatic injury (e.g. encephalopathy, nausea, vomiting, pruritus, severe fatigue, icterus, etc.) without laboratory results (ALT, AST, total bilirubin, INR) available, the Investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of the hepatic injury alert, the procedures described in the DILI checklist should be followed.

5.2.6.1.5 Intensity (severity) of adverse events

The intensity (severity) of AEs should be classified and recorded in the eCRF according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 dated 27 November 2017 [R18-1357].

5.2.6.1.6 Causal relationship of adverse events

Medical judgement should be used to determine the relationship between the AE and the BI investigational compound, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant therapy, concomitant diseases and relevant history.

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 trial drug concerned).
- Continuation of the event despite the withdrawal of the medication, considering 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.
- There is an 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.

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 trial 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).

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the participant files . Per default SAEs/AESIs should be reported via the eCRF in the EDC system. If the EDC system is not or no longer available (e.g. after database lock), the BI paper SAE form should be used; please see Section 5.2.6.2.2. The following must be collected and documented:

- From signing the informed consent onwards until the individual participant's end of trial (= the End of Study [EoS] visit, please see Section 6.2.3): all AEs (serious and non-serious) and all AESIs.
- After the individual participant's end of trial:
  the investigator does not need to actively monitor the participant for new AEs but should only report any occurrence of cancer of new histology and trial drug related SAEs and trial drug related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call.

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the AE or SAE eCRF pages to the sponsor's unique entry point within 24 hours of becoming aware of the event, the country specific process will be specified 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 in addition.

With receipt of any further information to these events, follow-up reports have to be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after individual participant'send of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

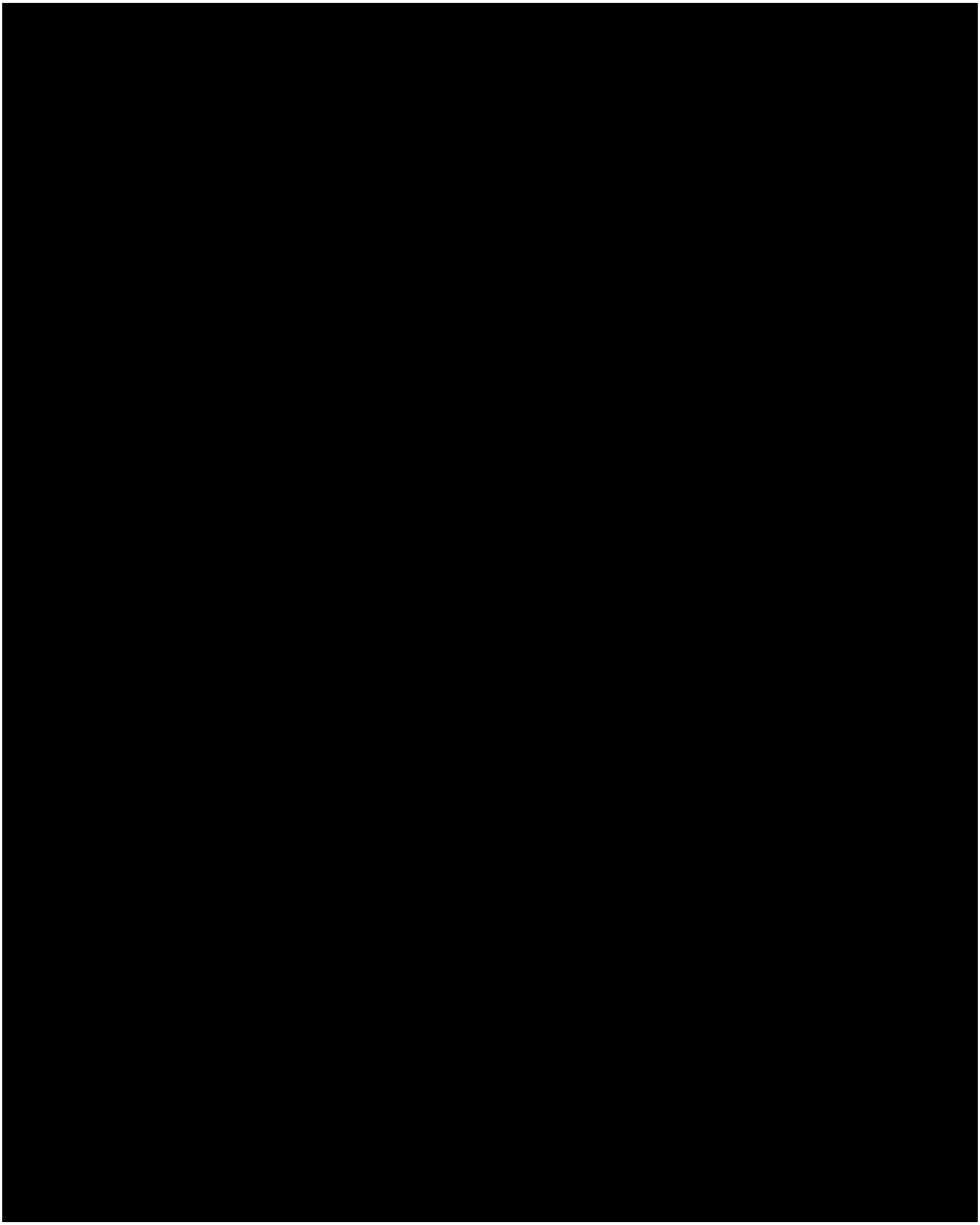
Should the EDC system not be available for more than 24 hours, reporting must occur via the BI paper SAE forms.

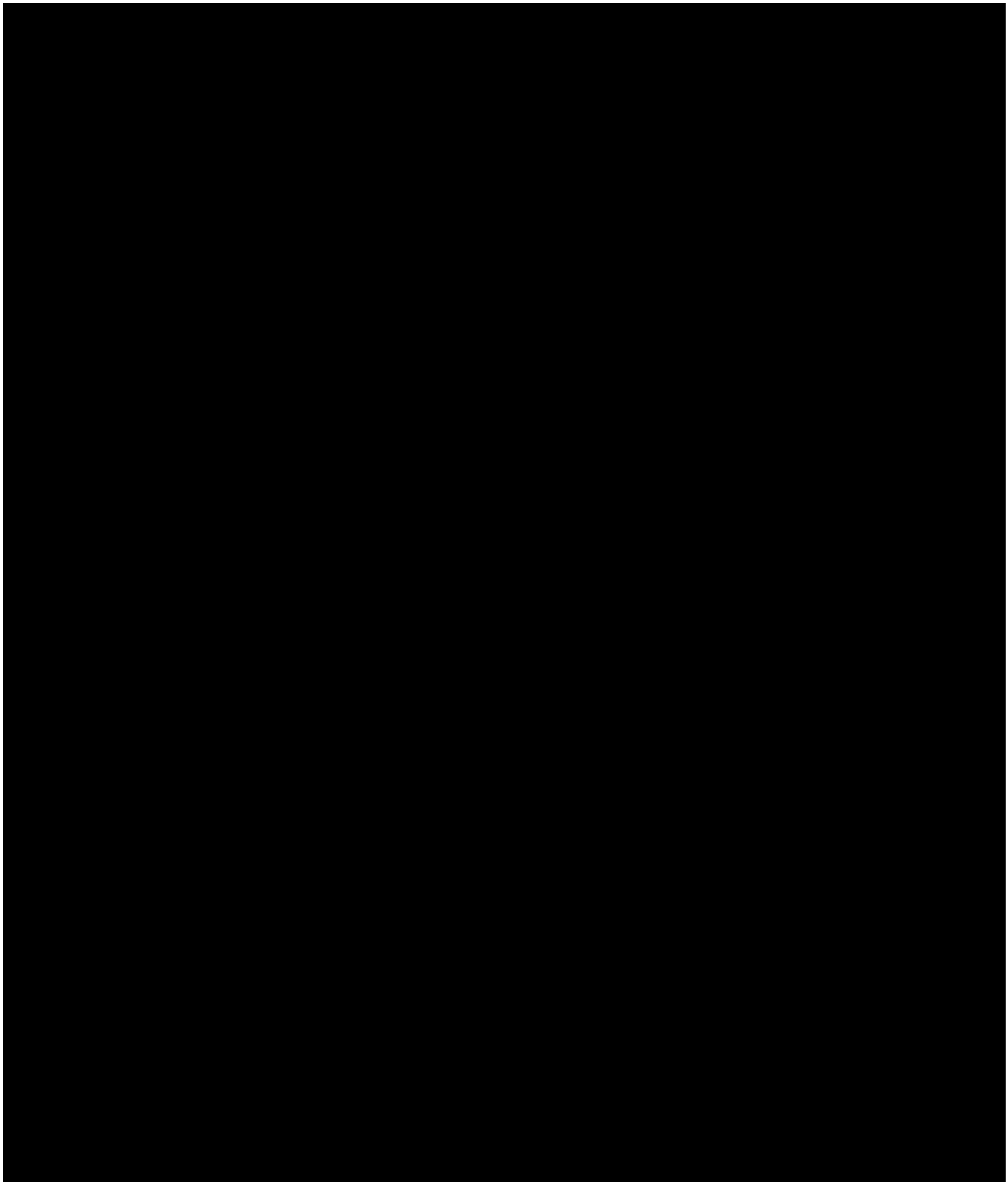
5.2.6.2.3 Pregnancy

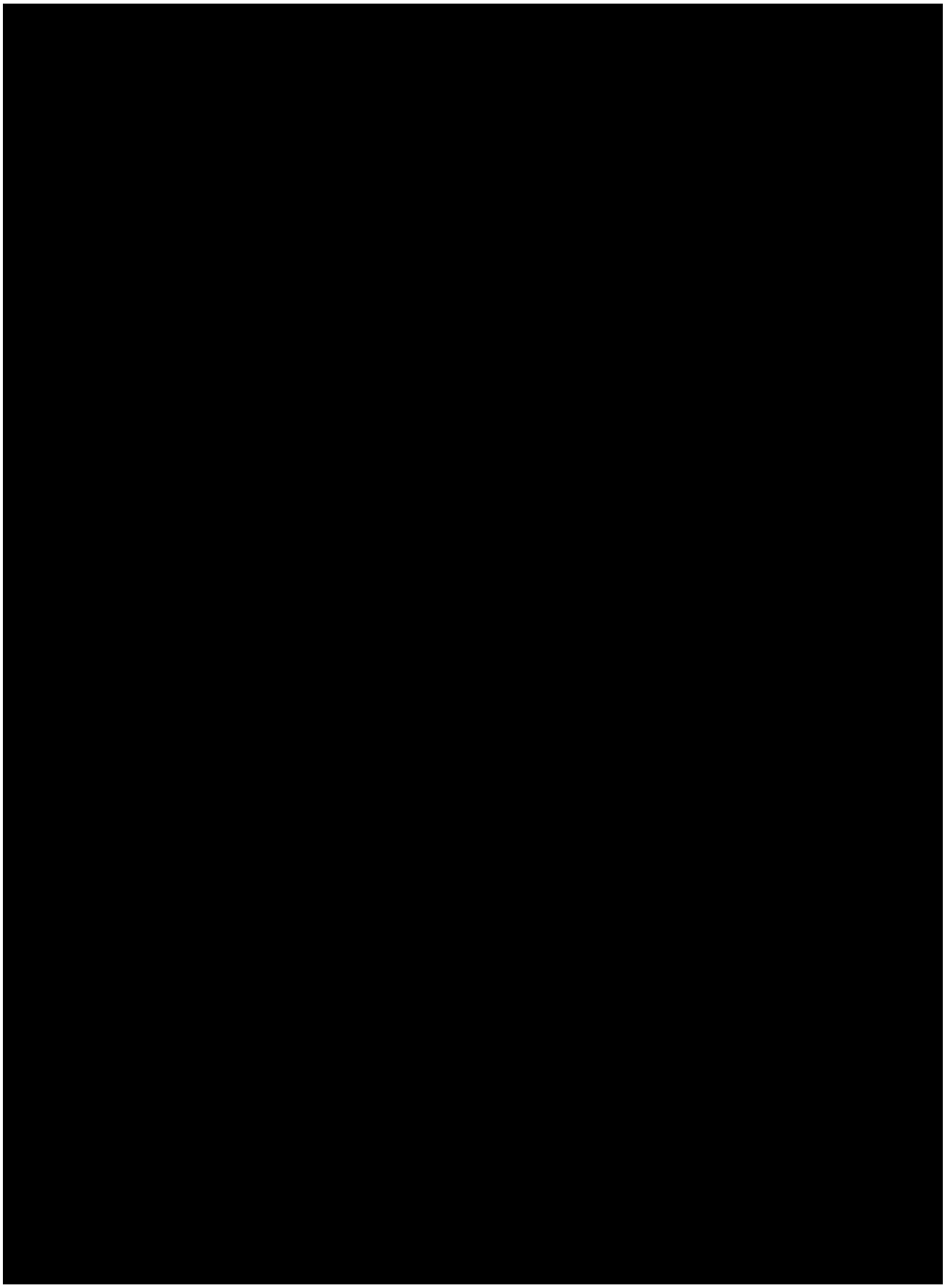
In rare cases, pregnancy might occur in a clinical trial. Once a trial participant has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy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

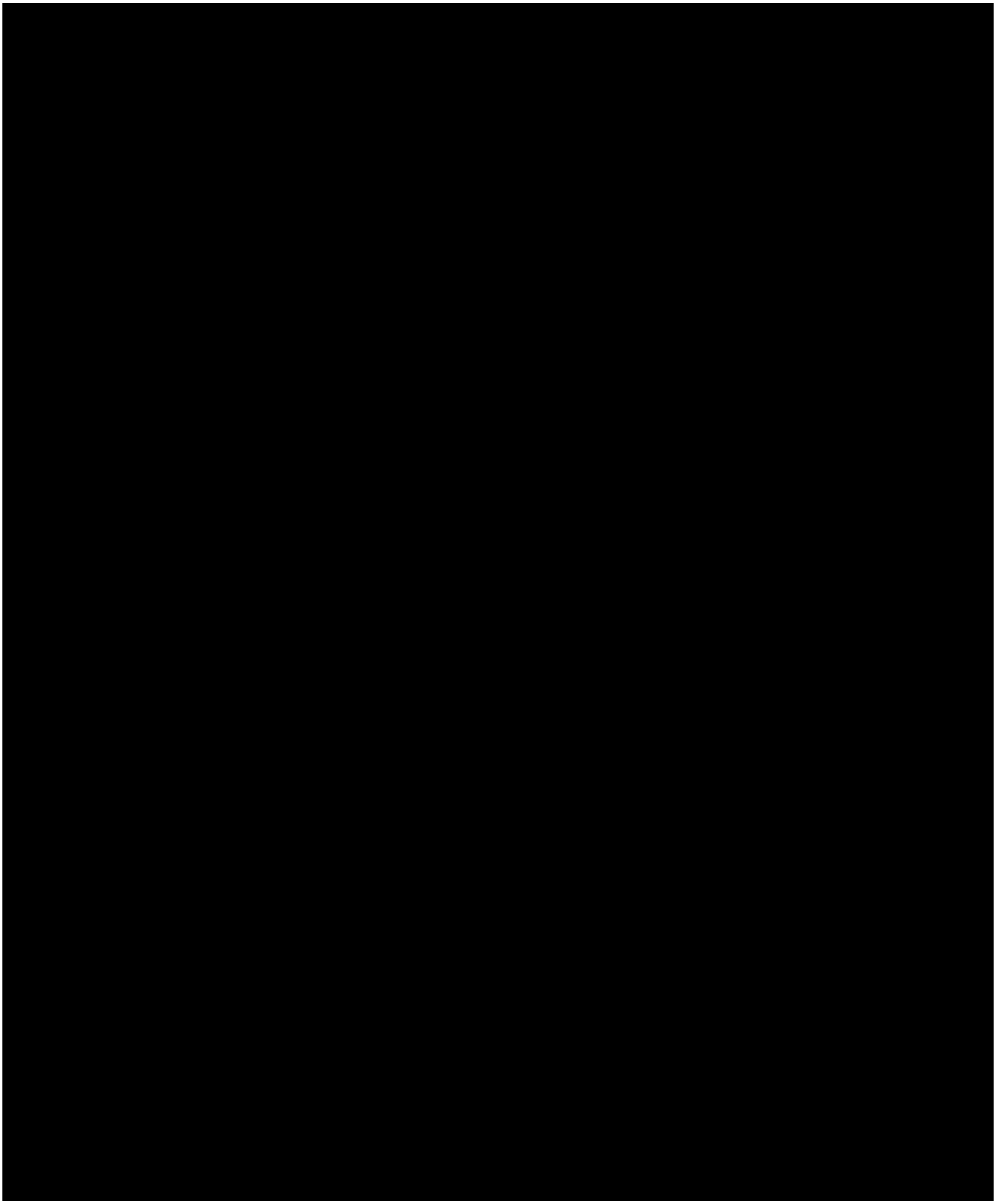
Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner.
The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Studies (Part B).
The ISF will contain the Pregnancy Monitoring Form for Studies (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Studies is to be completed. However, a SAE and/or AESI associated with the pregnancy it must be reported as described in Section 5.2.6.2.2.









5.5 BIOBANKING

Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Biobanking will only occur after a separate biobanking informed consent has been given in

accordance with local ethical and regulatory requirements. For China, samples for biobanking will not be collected, due to regulatory restrictions.

5.5.1 Methods and timing of sample collection

For all biospecimens collected, detailed instructions on sampling, preparation, processing, shipment and storage will be provided in the central laboratory manual in the ISF. Plasma and serum for biobanking will be collected at the timepoints specified in the Flow Chart. Biobanking sampling requires a consistent status from one sample to another in terms of the fasting vs non-fasting; a fasting status has been chosen for this trial.

5.6 OTHER ASSESSMENTS

5.7 APPROPRIATENESS OF MEASUREMENTS

This trial includes standard efficacy and safety measurements routinely performed in clinical practice in the chosen trial populations, as well as non-standard measurements. Refer to Section 1.4.2 for further details. Also refer to Section 3.2 for justification regarding the choices made.

6. INVESTIGATIONAL PLAN

In the event of force majeure or other disruptive circumstances (e.g. pandemic, war) the execution of the investigational plan as per this clinical trial protocol may not be feasible. With the consent of the participant, the sponsor and investigator may agree on alternative, back-up or rescue methodology which may include but will not be limited to virtual trial participant visits and assessments, home healthcare nurse visits, direct-to-participant/direct-from-participant shipments of trial treatment or bio-sample pick up from the participant's home. The implementation of these measures will depend on participant's consent, operational feasibility, local law and regulations. If alternative methodology is implemented, the deviations from the original plan will be precisely documented.

6.1 VISIT SCHEDULE

All visits should be scheduled according to the Flow Chart. Each visit date (with its permitted time window) should be calculated in relation to the day of randomization (i.e. Day 1). During the dose titration period of the trial (i.e. from Visit 2 to Visit 4), scheduled trial visits must be at least 7 days apart, since a trial participant must have taken the preceding dose of BI 685509 for at least 7 consecutive days before up-titration occurs (refer to Section 4.1.4). For this reason, if the permitted time window (+2 days) is applied to Visit 3, the permitted time window must also be applied to Visit 4 (+2 days). Missed visits should be re-scheduled as soon as possible ideally within the permitted time window for that visit. If any visit has to be rescheduled, subsequent visits should follow the original visit schedule. Unscheduled visits can be performed at the discretion of the Investigator at any time for safety reasons or, for instance, to provide trial medication (e.g. a re-start of BI 685509 following treatment interruption).

All visits will take place at the investigational site, and ideally they should be performed in the morning. In the randomised treatment period, on the morning of a visit, the trial medication will be administered as part of the visit. Therefore, on these days, trial participants should be instructed not to take their morning dose in advance of their clinic visit (refer to Section 4.1.4). [redacted]

The fasting status of a trial participant should be in accordance with the Flow Chart and will be recorded in the eCRF. Trial participants who fail to follow the afore-mentioned instructions should have the visit re-scheduled as soon as possible, ideally on the following day.

In the event of force majeure or other disrupting circumstances (refer to Section 6), physical trial participant visits to the sites may not be feasible or may need to be restricted to ensure trial participant safety. Based on a thorough assessment of the benefits and risks, the following visit may be performed at the trial participant's home, remotely (by phone) or as a combination of home and remote visit:

- Visit 6

When scheduling such visit every effort should be made to ensure a continuous supply of trial medication for the trial participant, whilst also taking into account that the next kit(s) of trial medication may need to be shipped from the site to the trial participant's home (refer to Section 4.1.4) and, that medical pre-requisites should be performed and confirmed prior to shipment of new supplies.

All deviations from the original schedule of visits will be documented and the implications considered for the analysis of the trial data.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

At each visit, assessments should be performed as indicated in the Flow Chart and as detailed in Section 5.

In the treatment period, all assessments should be performed before the trial medication is taken. Exceptions to this are post-dose vital signs and ECGs [redacted]. Once the trial medication is administered / once all visit assessments are complete that require a fasting status, trial participants may eat as normal [redacted]

Vital signs measurements should always precede the ECG, and the ECG should always be measured before any blood samples are taken (refer to the Flow Chart and Sections 5.2.2 and 5.2.4).

In the event of force majeure or other disrupting circumstances the visit indicated in Section 6.1 may have to be performed at the trial participant's home, remotely (by phone) or as a combination of home and remote visit. At this visit, the following assessments can be performed at the trial participant's home or remotely:

- concomitant therapy
- IRT call
- dispense trial medication
- train trial participant / provide refresher training / dispense / review results (home BP and HR monitoring; [redacted]
- all AEs / SAEs / AESIs
- compliance check

Trial medication will not be collected at the visit performed remotely. Instead, the medication should be collected when the trial participant next visits the site, or when a visit is performed at the trial participant's home (see below).

The following assessments can be performed at the trial participant's home:

- anthropometric measures
- vital signs
- physical examination
- resting 12-lead ECG (using a portable ECG machine)

- collect trial medication

If safety laboratory sampling via the central laboratory is not possible from the investigational site in the event of force majeure or other disrupting circumstances (and is instead performed at the trial participant's home), analyses can be performed at a local laboratory. The results of the safety laboratory tests must be transferred to the Investigator who must ensure a medical review and document any clinically relevant safety issues as AEs. For a list of "minimum required safety laboratory parameters" refer to Section 5.2.3 and Table 5.2.3: 2.

All deviations from the original schedule of assessments as defined in the Flow Chart will be documented and the implications considered for the analysis of the trial data.

6.2.1 Screening period (Visit 1a and 1b)

No trial procedures should be performed unless the trial participant has consented to take part in the trial. Once a trial participant has consented, he / she is considered to be enrolled in the trial and to have started screening. The trial participant should be recorded on the enrolment log and be registered in the IRT system as a screened trial participant. Trial participants who are not eligible to proceed to Visit 2 (i.e. they fail screening at either Visit 1a or 1b) should be registered as a screen failure in the IRT system and the eCRF and no further follow-up is required. Also refer to Section 3.3 for guidance regarding re-screening (and re-testing) during the screening period.

The screening period is defined as the period prior to randomisation and the first administration of trial medication. It consists of 2 visits (refer to Flow Chart), namely Visit 1a and Visit 1b; these visits should ideally be completed within a period of 4 weeks, (i.e. Day 1, Visit 2). There is no minimum duration for the screening period. A trial participant can proceed from one visit to the next within the screening period as soon as all results from the previous visit are available and if he / she remains eligible for the trial.

At Visit 1a demographic information will be collected. This includes the following:

- age on the day of informed consent (in years)
- sex (male / female in order to describe the trial participant`s sex at birth)
- for female trial participants: of childbearing potential yes / no in order to characterise the trial participant population and as a basis for contraception requirements
- ethnicity and race in order to sufficiently characterise the trial participant population, to support possible subgroup analyses if needed, and to support the calculation of the kidney function via the CKD EPI formula which requires a trial participant to be classified as black or non-black (unless not acceptable according to local regulations)

Baseline Conditions and Medical History

Information with respect to medical history / baseline conditions will also be collected at Visit 1a (e.g. relevant chronic diseases, current observable conditions and other relevant conditions, based on Investigator judgement, which may not be observable on the day of the

examination [e.g. because the trial participant is receiving concomitant therapy to treat the condition]). This includes any new clinically relevant findings identified during the screening period.

6.2.2 Treatment period(s)

If a trial participant is deemed eligible for the trial following Visits 1a and 1b, the trial participant will be randomised at Visit 2 (Day 1) by using the IRT system. All Visit 2 assessments (refer to the Flow Chart) should have been completed prior to administration of the first dose of trial medication; exceptions are the post-dose vital signs and ECGs [redacted] Each trial participant can be randomised only once into the trial. The randomised treatment period starts with Visit 2 and ends when a trial participant reaches the EoT visit (refer to the Flow Chart). The last dose of BI 685509 will be administered in the evening of the day before the EoT visit.

Trial participants will be assessed regularly at scheduled visits as specified in the Flow Chart. During the dose titration phase of the treatment period (refer to Section 4.1.4), scheduled visits are more frequent. It is of particular importance that the time window for these visits is adhered to since the trial participant must have taken the preceding dose of BI 685509 for at least seven consecutive days before any up-titration occurs (refer to Sections 4.1.4, 4.1.4.1 and 4.1.4.2). Unscheduled visits may also be arranged where necessary; assessments completed during an unscheduled visit will depend on the circumstances under which the visit was planned, and should be based on Investigator judgement.

[redacted] Trial participants should also be reminded to bring [redacted] and the electronic BP and HR monitoring device with them to each trial visit (refer to Sections 5.2.2.1 and 5.6.1). Refresher training should be provided as required.

At every dispensing visit in the trial (refer to Flow Chart), an IRT call should be made.

6.2.2.1 End of treatment / Early discontinuation visit

Patients who successfully complete the entire 8 week treatment period should have the assessments for the EoT visit performed as indicated in the Flow Chart. Such patients should be registered as completed in the IRT system. End of trial medication must also be recorded on the corresponding eCRF.

For patients who discontinue trial medication prematurely (for whatever reason), an ED visit (refer to the Flow Chart) should be completed instead of the planned treatment period visit (refer to Section 3.3.4.1). Ideally the ED visit should be performed within seven days of discontinuing the trial medication. The assessments performed at the ED visit should be in accordance with the Flow Chart, with the following exceptions:

- HVPG: not required
- [redacted]
- [redacted]
- [redacted]
- biobanking sampling: not required

Patients who discontinue treatment early should be registered as discontinued in the IRT system. End of trial medication must also be recorded on the corresponding eCRF.

At the EoT and / or ED visit, patients should be reminded about restrictions (refer to Section 4.2.2) that still need to be observed up until the EoS visit (refer to Section 6.2.3). Home BP and HR monitoring should continue between the EoT / ED visit and the EoS visit.

6.2.3 Follow-up period and trial completion

An EoS visit should be scheduled 2 weeks after an EoT and / or ED visit (refer to the Flow Chart and Section 3.3.4.1); participation in the trial is over once this visit has been completed; completion must be recorded on the corresponding eCRF.

When an EoS visit is performed after an ED visit, the assessments performed at the EoS visit should be in accordance with the Flow Chart, with the following exceptions:

[redacted]

For an individual patient, trial completion is defined as completion of the EoS visit within the specified time window and who has not discontinued trial medication prematurely.
Following an EoS visit, the patient will return to standard medical care.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

In this trial, the primary endpoint is the percentage change in HVPG from baseline (measured in mmHg) after 8 weeks of treatment. The purpose of this trial is to demonstrate the short-time clinical activity of BI 685509 on trial participants with CSPH in decompensated cirrhosis after the first decompensation event.

7.1 NULL AND ALTERNATIVE HYPOTHESES

Statistical testing is not planned for this trial. All analyses will be descriptive in nature. The endpoints will be investigated. However, it is not planned to test a statistical hypothesis with regards to these variables in a confirmatory matter. Instead, they will be described and evaluated by descriptive statistical methods.

7.2 PLANNED ANALYSES

7.2.1 General considerations

The analyses will be performed based on the following analysis sets:

- **Enrolled set (ES)** – this analysis set includes all trial participants having signed informed consent and who were eligible for inclusion into the trial. The ES will be used for analyses of trial participant disposition
- **Randomised set (RS)** – this analysis set includes all enrolled trial participants that were randomised to the trial medication. The RS will be used for demographic and baseline disease characteristics presentation
- **Treated set (TS)** – the treated set includes all trial participants who were randomised to the trial medication and were treated with at least one dose. The TS will be used for all safety analyses
- **Full analysis set (FAS)** – this analysis set includes all enrolled or randomised trial participants who received at least one dose of trial medication and have a baseline measurement for the primary endpoint recorded. The FAS will be used for the efficacy analyses

Further analysis sets will be defined in the TSAP, if needed.

Efficacy analyses will be performed based on the planned treatment (i.e. the treatment assignment at randomisation). Safety analyses will be based on the actual treatment received at the enrolment/randomisation visit.

Unless otherwise stated, baseline is defined as the latest measurement before the first trial medication intake.

[redacted]

7.2.2 Handling of Intercurrent Events

The expected intercurrent events of interest in this trial are:

- use of the following restricted concomitant therapy:
  - NO-sGC-cGMP pathway activating therapies like NO-donors (e.g. glyceryl trinitrate, isosorbide di- or mono-nitrate, molsidomine), PDE-5-inhibitors (e.g. sildenafil, tadalafil, and vardenafil), non-specific PDE inhibitors such as dipyridamole and theophylline, or sGC-stimulators (e.g. riociguat)
- new onset of / dose change in existing NSBB / carvedilolconcomitant therapy
- occurrence of a decompensation event
- Premature discontinuation of assigned trial medication

The strategies for handling intercurrent events in this trial are as follows:
Treatment Policy: This is the effect of randomizing trial participants to a treatment arm regardless of treatment actually being taken. All intercurrent events will be handled according to the treatment policy approach as defined in ICH E9(R1).

Each analysis will reference the strategy for handling intercurrent events that it will be estimating. The estimand for each main analysis in this protocol is the combination of the relevant detailed clinical objective from Section 2.1 and this strategy.

Handling of the intercurrent events that are not listed above will be decided by the review and will be documented in the TSAP.

7.2.3 Primary objective analyses

The primary endpoint (refer to Section 2.1.2) will be analyzed using an ANCOVA model in the FAS without imputing the missing data.

The model is as follows:

Percentage change of HVPG from baseline at Week 8 = overall mean
+ HVPG baseline
+ treatment + use of NSBBs or carvedilol
+ type of first decompensation event
+ random error

This model includes effects accounting for the following sources of variation: 'treatment', 'use of NSBBs or carvedilol' and 'type of first decompensation event' are a fixed classification effects, and 'HVPG at baseline' is a linear covariate. The random error is assumed to be normally distributed with mean 0 and unknown variance σ^2.
The analysis will only be used for estimation of treatment effects without hypothesis testing. Trial participants will be analysed according to the stratum to which they belong (regardless of any mis-assignment to treatment based on identification of the wrong stratum), as such an error occurs before randomisation and is therefore consistent with regulatory guidance. Procedures to follow if the analysis fails to converge will be described in the TSAP.

7.2.3.1 Sensitivity Analyses

Sensitivity analyses may be performed and will be described in more detail in the TSAP, if applicable.

7.2.3.2 Subgroup Analyses

Any subgroup analyses planned for this trial will be described in the TSAP, if applicable.

7.2.4 Secondary objective analyses

Unless otherwise stated, only descriptive statistics will be presented for the secondary endpoints defined in Section 2.1.3. The percentage of trial participants who have experienced the events of interest for secondary endpoints will be presented.

7.2.5 Further objective analyses

Only descriptive statistics will be presented for further endpoints (defined in Section 2.2.2).

7.2.6 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events

with an onset between start of treatment and end of the REP, a period of 7 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

Safety analyses will be done by “treatment at onset” principle. All treated trial participants will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the REP. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) at database lock.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of trial participants with abnormal values or clinically relevant abnormal values.

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

[redacted]

7.2.8 Interim Analyses

No interim analysis is planned but a Data Monitoring Committee (DMC) will be in place with tasks as described in section 8.7. Full details will be specified in the DMC charter. The primary role of the DMC is the ongoing evaluation of safety.

7.3 HANDLING OF MISSING DATA

[redacted]

No imputation of missing data is planned for the remaining endpoints. If a trial participant misses a visit, the missing data will not be imputed.

7.4 RANDOMISATION

BI will arrange for the randomisation and the packaging and labelling of trial medication. The trial will be performed as a double-blind design with respect to placebo and active BI 685509. Trial participants will be randomised in blocks to one of the two treatment groups in a 1:1 ratio. The randomisation will be stratified by use (or not) of NSBBs or carvedilol and type of first decompensation event (ascites or variceal haemorrhage) (refer to Section 3.1).

The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the assigned treatment will be reproducible but at the same time non-predictable. The block size will be documented in the CTR. Access to the codes will be controlled and documented.

7.5 DETERMINATION OF SAMPLE SIZE

It is planned to enrol 40 trial participants in total in this trial: 20 trial participants per treatment group (active vs. placebo).

It will be considered as a positive signal if a mean percentage reduction of HVPG from baseline after 8 weeks of treatment of at least 15% is observed. it was assumed that the mean percentage reduction of HVPG from baseline at week 8 would be: 0% and 20% for placebo and BI 685509, respectively(with a standard deviation of 25% in each group) based on previous studies [R21-1984, R21-1945]. With the sample size of 40 (20 trial participants per treatment group), the probability to observe a mean percentage reduction of HVPG≥ 10% in BI 685509 is 89.3%. This probability would be only 26.5% in case that the mean percentage reduction of HVPG from baseline is 5%. Probabilities of achieving an assumed treatment effect within different scenarios are presented in Table 7.5: 1.

Table 7.5: 1 Scenarios of probabilities of achieving the assumed treatment effect

Scenarios	Assumption of mean percentage reduction in HVPG from baseline to week 8 [1,2]	Probability that the observed treatment effect is ≥ 10%
Positive	20%	89.3%
	15%	73.5%
Negative	5%	26.5%
	0%	10.3%

SD = 25%
N=20 per treatment group

The calculations were performed using R 4.1.2.

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

The trial will be carried out in compliance with the CTP, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for GCP, relevant BI SOPs, the EU directive 2001/20/EC, EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the CTP, the principles of ICH-GCP or applicable regulations as will be treated as "protocol deviation".

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

The Investigator will inform the Sponsor or delegate immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the CTP or of ICH-GCP.

The BI transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the Investigator and of the Sponsor with regard to publication of the results of this trial will be described in the Investigator contract. As a rule, no trial results should be published prior to finalisation of the CTR.

The certificate of insurance cover will be made available to the Investigator and the patients, and will be stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT 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 patient participation in the trial, written informed consent must be obtained from each patient (or the patient'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 patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The investigator or delegate must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.

The patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient 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.

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 participant protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, 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 trial participants will be provided by the sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements, the Investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. 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 eCRF must be consistent with the source data or the discrepancies must be explained. The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the Investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the Investigator must make at least one

documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

Copies of source documents necessary for e.g. HVPG central evaluation and hepatic injury adjudication will be provided to external Suppliers. Before sending or uploading those copies, the Investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number etc.) have been properly removed or redacted from any copy of the patients' source documents.

If the patient is not compliant with the CTP, any corrective action e.g. re-training must be documented in the patient file.

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

- patient identification: sex, year of birth (in accordance with local laws and regulations)
- patient participation in the trial (substance, trial number, patient number, date patient was informed)
- dates of patient's visits, including dispensing of trial medication
- medical history (including trial indication and concomitant diseases, if applicable)
- medication history
- AEs and AESIs (onset date [mandatory], and end date [if available]), including those identified from measurements within the home BP and HR monitoring equipment
- SAEs (onset date [mandatory], and end date [if available])
- concomitant therapy (start date [where required], dose / frequency [where required], changes)
- originals or copies of laboratory results and other imaging or testing results (e.g. HVPG, ultrasound [redacted], with proper documented medical evaluation (in validated electronic format, if available)
- ECG results
- [redacted]
- completion of patient's participation in the trial (end date; in case of early discontinuation, the reason for it should be documented if available)
- prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a CTP) to support inclusion / exclusion criteria does not make the patient eligible for the clinical trial

8.3.2 Direct access to source data and documents

The investigator/institution will allow site trial-related monitoring, audits, IRB/IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must always be available for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified

by direct comparison with the source documents described in Section 8.3.1. The sponsor or delegate will also monitor compliance with the protocol and GCP.

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war; please see Section 6), site access may be restricted, thus limiting the ability to perform standard site monitoring activities on site such as on-site source data review and source data verification. Therefore, some of these activities may be performed remotely or replaced by centralized monitoring to the extent possible, based on a documented risk assessment and in alignment with local regulations.

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND TRIAL PARTICIPANT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of trial participant data in accordance with the principles 7 and 12 of the WHO GCP handbook.

To ensure confidentiality of records and personal data, only pseudonymised data will be transferred to the sponsor by using a participant identification number instead of the trial participant's name. The code is only available at the site and must not be forwarded to the sponsor. In case participant's records will be forwarded e.g. for SAE processing or adjudication committees, personal data that can identify the trial participant will be redacted by the site prior to forwarding. Access to the participant files and clinical data is strictly limited: personalised treatment data may be given to the trial participant's personal physician or to other appropriate medical personnel responsible for the trial participant'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.

A potential data security breach will be assessed regarding the implications for rights and privacy of the affected person(s). Immediate actions as well as corrective and preventive actions will be implemented. Respective regulatory authorities, IRBs/IECs and trial participants will be informed as appropriate.

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

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

- Sample and data usage have to be in accordance with the separate biobanking informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation [redacted] ensures compliant usage
- [redacted]
- Samples and/or data may be transferred to third parties and other countries as specified in the biobanking ICF

8.6 TRIAL MILESTONES

The first act of recruitment represents the start of the trial and is defined as the date when the first trial participant in the whole trial signs informed consent.
The end of the trial is defined as the date of the last visit of the last trial participant in the whole trial ("Last Participant Completed").

The "Last Participant Last Treatment" (LPLT) date is defined as the date on which the last trial participant in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site.
Early termination of the trial is defined as the premature termination of the trial due to 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 IEC/competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all trial participants have completed the trial in all countries (EU or non-EU) to incorporate and consider all data 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 trial participant (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

Data Monitoring Committee:
A DMC will be established. Members of the DMC will be independent of BI, and will include physicians experienced in the treatment of the disease under investigation, and a statistician. The DMC will evaluate safety data, and receive efficacy data, significant safety concerns, and decisions from hepatic injury adjudication for evaluation. While DMC members may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial Regular DMC meetings will be held at specified intervals. The DMC will recommend continuation, modification or termination of the trial as detailed in the DMC charter. DMC recommendations, as well as the final BI decision, will be reported to the appropriate regulatory authorities / Health Authorities, IRBs / ECs, and to Investigators as requested by local law. The tasks and responsibilities of the DMC will be specified in the charter.

Hepatic injury Adjudication Committee:
An independent AC will be used to adjudicate certain hepatic injury events for severity and causal relationship with the trial medication. Events may either be defined by abnormal laboratory values and / or relevant AEs. They will be defined in the hepatic injury AC charter. For qualifying events, relevant source documents generated from any medical evaluations of these events will be requested. Relevant source documents might include laboratory values, histological analysis, reports from ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), hospital discharge letters and medical reports from other physicians.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The Investigators will have access to the BI web portal Clinergize to access documents provided by the Sponsor.

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

- manage the trial in accordance with applicable regulations and internal SOPs
- direct the clinical trial team in the preparation, conduct and reporting of the trial
- ensure appropriate training and information of Clinical Trial Managers, CRAs and Investigators of participating countries

In the participating countries the trial will be performed by the respective local or regional BI-organisation (Operating Unit) in accordance with applicable regulations and BI SOPs, or by a CRO based on a contract. The CRO will perform project management, clinical field monitoring, medical monitoring, and reporting.

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.

A central laboratory service, a central reading service for HVPG, an IRT supplier and other central services / equipment will be used / provided in this trial. Details will be provided in the respective manuals and will be available in the ISF.

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10. APPENDICES

10.2 REMOVAL OF INDIVIDUAL PATIENTS IN CASE OF INCREASED LIVER ENZYMES

Trial-specific procedures have been defined in case of increased liver enzymes after enrolment as outlined below. Baseline refers to Day 1.

- Normal aminotransferases at baseline

New elevations of aminotransferases to > 2 x ULN should be followed by a repeat testing within 48 to 72 hours. If elevations persist, other causes of aminotransferase elevations should be evaluated along with tests of hepatic function. If no other cause is identified, the patient should be monitored closely.

Treatment with trial medication should be discontinued if:

- ALT or AST increases to > 8 x ULN
- ALT or AST increases to > 5 x ULN for more than 2 weeks
- ALT or AST increases to > 3 x ULN and the increase is accompanied by a concomitant increase in total bilirubin to > 2 x ULN or INR to > 1.5
- ALT or AST increases to > 3 x ULN and the increase is accompanied by the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and / or eosinophilia (> 5%)

- Abnormal aminotransferases at baseline

If a patient develops elevations of ALT or AST to > 2 x baseline or total bilirubin 1.5 x baseline values, the testing should be repeated within 48 to 72 hours. If elevations persist, then close observation (testing and physical examination 2 to 3 times a week) should be implemented and discontinuation of trial medication should be considered. Decision to discontinue the trial medication should be considered based on factors that include how much higher than baseline ALT and AST values were relative to ULN and how much the on-treatment ALT and AST values have increased relative to baseline, in addition to the elevation of total bilirubin or INR.

Treatment with trial medication should be discontinued if:

- baseline values were < 2 x ULN, and ALT or AST increases to > 5 x baseline values
- baseline values were ≥ 2 x ULN but < 5 x ULN, and ALT or AST increases to > 3 x baseline values
- baseline values were 5 x ULN, and ALT or AST increases to > 2 x baseline values
- ALT or AST increases > 2 x baseline values and the increase is accompanied by a concomitant increase in total bilirubin to > 2 x baseline value or INR concomitantly increases by > 0.2 (to prevent false positive results, another sample should be tested within 24 hours)
- patient (with any magnitude of aminotransferase elevation) develops signs and symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and / or eosinophilia (> 5%)

Patients should be followed up until resolution of symptoms or signs in the above stated situations [P09-12413]. After resolution or stabilisation the patient should complete the procedures for the EoT and EoS visits as outlined in the Flow Chart, Section 3.3.4.1 and Sections 6.2.2 and 6.2.3.

10.3 CHILD-TURCOTTE-PUGH CLASSIFICATION

Table 10.3: 1 Child-Turcotte-Pugh scoring system to assess severity of liver disease [R18-3281]

Clinical and laboratory criteria	Points[1]		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL) Bilirubin (µmol/L)	<2 <34.2	2-3 34.2-51.3	>3 >51.3
Albumin (g/dL) Albumin (g/L)	>3.5 >35	2.8-3.5 > 28-35	<2.8 <28
Prothrombin time (seconds prolonged) Or INR[2]	<4 <1.7	4-6 1.7-2.3	>6 >2.3

[1]Child-Turcotte-Pugh class obtained by adding the score for each parameter above (total score)
Child-Turcotte-Pugh A = 5 to 6 points (mild)
Child-Turcotte-Pugh B = 7 to 9 points (moderate)
Child-Turctotte-Pugh C = 10 to 15 points (severe)
[2]INR (measured by the central laboratory) will be used by the site in this trial to calculate the Child-Turcotte-Pugh score

10.4 TRIAL PARTICIPANT FEEDBACK

Optional Trial Participant Feedback Questionnaires:
This trial will include an option for participants to complete anonymized questionnaires, 'Trial Participant Feedback Questionnaire', to provide feedback on their clinical trial experience. Individual participant level responses will not be reviewed by investigators. Responses will be used by the sponsor to understand where improvements can be made in the clinical trial process. These questionnaires will not collect data about the participant's disease, symptoms, treatment effect, or AEs and therefore will not be part of the trial data or clinical trial report. The questionnaires will be implemented after local regulatory approval and after consent of the trial participant. Providing feedback is optional and not required for participation in the trial.

11. CONFIDENTIALITY STATEMENT DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of Amendment		29-Nov-2023
EudraCT No. **EU Trial No.**		2023-506083-13-00
BI Trial No.		1366-0055
BI Investigational Medicinal Product		BI 685509
Title of protocol		Randomised, double-blind, placebo-controlled and parallel group trial to investigate the effects of one dose (up-titration to a fixed dose regimen) of oral BI 685509 on portal hypertension after 8 weeks treatment in patients with clinically significant portal hypertension (CSPH) in decompensated cirrhosis after their first decompensation event, who are stabilized CTP 5-7
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Main exclusion criteria: “primary biliary sclerosis” replaced by “primary biliary cholangitis”.
Rationale for change		Correction/clarification
Section to be changed		ABBREVIATIONS AND DEFINITIONS
Description of change		Deletion of abbreviation : SARS-CoV-2 : Severe Acute Respiratory Syndrome CoronaVirus 2
Rationale for change		No reference of SARS-CoV2 is mentioned in the text
Section to be changed		3.3.3 Exclusion criteria
Description of change		Deletion of the bold text : Exclusion Criteria #1.History of cholestatic chronic liver disease (e.g. primary biliary **~~sclerosing~~** cholangitis,)
Rationale for change		Correction / clarification
Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		Deletion of the following paragraph : Ideally, the trial participant should attend all remaining visits. Should the trial participant not agree, at least phone contacts should occur at the scheduled visit time points, should that not be acceptable, a phone contact once or at the end of the planned observation period should occur to collect the most relevant information: vital status, outcome events, adverse

		events (please see section 5.2.6.2.1), or last contact date in case of lost to follow-up."
Rationale for change		deletion as it is no applicable for our study
Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		Text added : • the trial participant develops an AE: ○ CTCAE Grade 3 or higher and the AE was assessed by the Investigator as related to the trial treatment; OR ○ CTCAE grade 4 or higher regardless of attribution to the trial treatment
Rationale for change		Request from Health Authority
Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		Text added : Boehringer Ingelheim will closely monitor and medically review all adverse events CTCAE Grade 3 and higher. BI will pause the enrollment of new patient in the trial and ensure the clinical data is reviewed by the data monitoring committee (DMC) for safety before proceeding with the trial if one of the following occurs: 1. more than two patients develop a CTCAE grade 3 or higher in the same category; OR 2. two or more patients meet the individual patient stopping criteria related to adverse event
Rationale for change		Request from Health Authority
Section to be changed		5.2.3 Safety laboratory parameters /
Description of change		Text added in Table 5.2.3: 1 Safety laboratory tests: - Haematology: Haemoglobin - RBC count / erythrocytes - Automatic WBC differential (absolute and percentage) - Brain Natriuretic Peptide (BNP)
Rationale for change		Correction as these parameters were mentioned in different section of the protocol but not listed in the table
Section to be changed		Table 5.2.3: 1 Safety laboratory tests
Description of change		Correction of the Superscript number of the following parameters: Alpha fetoprotein[1] correct to Alpha fetoprotein4 CK-MB[2] corrected to CK-MB[1] Phosphatidylethanol (PEth)[3] corrected to Phosphatidylethanol (PEth)[2] Troponin I[2] corrected to Troponin I[1]

		Infections screening6 corrected to Infections screening[4]
Rationale for change		Correction
Section to be changed		Table 5.2.3: 1 Safety laboratory tests
Description of change		The text in bold has been added to footnote#2 and deleted in footnote #3 i.) Footnote #2 : Not performed at screening (Visit 1a). **PEth, an alcohol-specific biomarker, will be measured during the treatment period for data analysis purposes** ii.) Footnote#3 : Not performed at screening (Visit 1a) ~~**or EoS; collect seated after patient seated for at least 5 to 15 minutes, and once patient has been out of bed for at least 2 hours**~~
Rationale for change		i. Clarification for the purpose of the assessment of PEth ii. Correction as it not applicable for the safety parameters linked to superscript 3
Section to be changed		7.2.1 General considerations
Description of change		Deletion of bold text : this analysis set includes all enrolled trial participants that were ~~**entered or**~~ randomised
Rationale for change		Administrative correction

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Biostatistics	[redacted]	30 Nov 2023 12:05 CET
Approval-Clinical Trial Leader		30 Nov 2023 12:43 CET
Approval-Team Member Medicine		30 Nov 2023 14:27 CET
Approval-Clinical Trial Leader		30 Nov 2023 14:42 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed