Clinical Trial Protocol

	Document Number:	**c34798591-07**
EudraCT No. **EU Trial No.**	2021-001285-38	
BI Trial No.	1366-0021	
BI Investigational Medicinal Product	BI 685509	
Title	Randomised, double-blind, placebo-controlled and parallel group trial to investigate the effects of two doses (up-titration to a fixed dose regimen) of oral BI 685509 on portal hypertension after 24 weeks treatment in patients with clinically significant portal hypertension (CSPH) in compensated cirrhosis	
Lay Title	A study to test whether two different doses of BI 685509 help people with liver cirrhosis and high blood pressure in the portal vein (main vessel going to the liver)	
Clinical Phase	II	
Clinical Trial Leader	[redacted] Tel: [redacted] Fax: [redacted]	
Coordinating Investigator	[redacted] Tel: [redacted] Fax: [redacted]	
Current Version and Date	Version 7.0, 02 Nov 2023	
Original Protocol Date	Version 1.0, 27 May 2021	

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original Protocol date	27 May 2021
Revision date	02 Nov 2023
BI trial number	1366-0021
Title of trial	Randomised, double-blind, placebo-controlled and parallel group trial to investigate the effects of two doses (up-titration to a fixed dose regimen) of oral BI 685509 on portal hypertension after 24 weeks treatment in patients with clinically significant portal hypertension (CSPH) in compensated cirrhosis
Coordinating Investigator	[redacted]
Trial sites	Multi-centre trial
Clinical phase	II
Trial rationale	In this Phase II trial the efficacy of treatment in patients with CSPH (defined by the presence of varices and hepatic venous pressure gradient [HVPG] ≥ 10 mmHg), in compensated alcohol-related cirrhosis, will be assessed. This will be the first trial in the clinical development of BI 685509 where patients will be treated for 24 weeks, and where the portal pressure will be assessed quantitatively via HVPG measurements. The trial will evaluate both short-term and long-term efficacy. The long-term assessment will be used to rule out any adaptation to sGC activation on portal pressure on chronic treatment. The trial will also provide supportive evidence for the planned Phase III development
Trial objectives	The trial will compare two doses of BI 685509 with placebo, on top of standard of care, in patients with CSPH in compensated alcohol-related cirrhosis. The primary objective is to estimate the mean difference between treatment groups with placebo in percentage change in HVPG from baseline measured after 24 weeks. Safety and tolerability will also be investigated.
Trial endpoints	The **primary** endpoint is the percentage change in HVPG from baseline (measured in mmHg) after 24 weeks of treatment. **Secondary** endpoints include: • percentage change in HVPG from baseline (measured in mmHg) after 8 weeks of treatment • response defined as > 10% reduction from baseline HVPG (measured in mmHg) after 8 weeks of treatment • response defined as > 10% reduction from baseline HVPG (measured in mmHg) after 24 weeks of treatment

	• occurrence of one or more decompensation events (i.e. ascites, variceal haemorrhage [VH], and / or overt hepatic encephalopathy [HE]) during the 24 week treatment period • occurrence of CTCAE grade 3 (or higher) hypotension or syncope based on Investigator judgement, during the first 8 weeks of the treatment period • occurrence of CTCAE grade 3 (or higher) hypotension or syncope based on Investigator judgement, during the 24 week treatment period • occurrence of discontinuation due to hypotension or syncope during the first 8 weeks of the treatment period • occurrence of discontinuation due to hypotension or syncope during the 24 week treatment period
Trial design	Randomised, double-blind, parallel group, placebo-controlled comparison of treatment with BI 685509 over 24 weeks
Total number of patients randomised	78
Number of patients per treatment group	26
Diagnosis	Patients with CSPH in compensated alcohol-related cirrhosis
Main inclusion and exclusion criteria	**Main inclusion criteria** • 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) • clinical signs of CSPH as described by either one of the points below: o documented endoscopic proof of oesophageal varices and / or gastric varices at screening (Visit 1b) or within 6 months prior to screening (Visit 1b) o documented endoscopic-treated oesophageal varices as preventative treatment • CSPH defined as baseline HVPG ≥ 10 mmHg (measured at Visit 1c), based on a local interpretation of the pressure tracing • diagnosis of compensated alcohol-related cirrhosis. Diagnosis must be based on histology (historical data is acceptable) or on clinical evidence of cirrhosis (e.g. platelet count < 150 x 10^9/L [150 x 10^3/µL], nodular liver surface on imaging or splenomegaly) • 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) • willing and able to undergo HVPG measurements per protocol (based on Investigator judgement) • 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

	• if receiving 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 **Main exclusion criteria** • previous clinically significant decompensation events (e.g. ascites [more than perihepatic ascites], VH and / or apparent HE) • history of other forms of chronic liver disease (e.g. non-alcoholic steatohepatitis [NASH], Hepatitis B virus [HBV], untreated HCV, autoimmune liver disease, primary biliary cholangitis, primary sclerosing cholangitis, Wilson's disease, haemachromatosis, alpha-1 antitrypsin [A1At] deficiency) • alcohol-related liver disease (ARLD) without adequate treatment (e.g. lifestyle modification) or with ongoing pathological drinking behaviour (misuse / abuse based on Investigator judgement) • SBP < 100 mmHg and DBP < 70 mmHg at screening (Visit 1a) • Model of End-stage Liver Disease (MELD) score of > 15 at screening (Visit 1a) • hepatic impairment defined as a Child-Turcotte-Pugh score ≥ B8 at screening (Visit 1a) • ALT or AST > 5 times upper limit of normal (ULN) at screening (Visit 1a) • eGFR (CKD-EPI formula) < 20 mL/min/1.73 m^2 at screening (Visit 1a) • alpha-fetoprotein > 50 ng/mL (> 50 µg/L) at screening (Visit 1a) history of clinically relevant orthostatic hypotension, fainting spells or blackouts due to hypotension or of unknown origin (based on Investigator judgement)
Test product	BI 685509
dose	Treatment group 1: [redacted] BI 685509 *BID* (maintenance dose) Treatment group 2: [redacted] BI 685509 *BID* (maintenance dose
mode of administration	Oral
Comparator product	Placebo
dose	Matching
mode of administration	Oral
Duration of treatment	24 weeks
Statistical methods	For the primary endpoint, restricted maximum likelihood estimation based on a mixed-effect for repeated measures analysis will be used to obtain adjusted means for the treatment effects. This model will include discrete fixed effects for treatment at each visit and use of NSBBs or carvedidol (yes / no) at baseline and continuous fixed effect for baseline HVPG at each visit. The analysis will only be used for estimation of treatment effects without performing statistical tests. 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]**	**1c[1]**	**2[2]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**EoT / ED[3]**	**EoS[3]**
Week	**-6**			**R**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**
Day	**-42**			**1**	**8**	**15**	**29**	**43**	**57**	**85**	**113**	**141**	**169**	**197**
Time window for visits (days)	**See footnote 1**			**N/A**	**+ 2**	**+ 2**	**+ 2**	**± 3**	**± 3**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**
Fasting status[4]	**NF**	**F**	**F**	**F**	**NF**	**NF**	**F**	**NF**	**F**	**NF**	**NF**	**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	x	x	x	x	x
Anthropometric measures[6]	x			x	x	x	x	x	x	x	x	x	x	x
Vital signs[7]	x			x[23]	x[23]	x[23]	x[23]	x	x	x	x	x	x	x
Physical examination[8]	x[22]			(x)	(x)	(x)	(x)	(x)	x	(x)	(x)	(x)	x	(x)
Resting 12-lead ECG[7]	x			x[23]	x[23]	x[23]	x[23]	x	x	x	x	x	x	x
Safety laboratory sampling	x			x	x	x	x		x	x	x	x	x	x
Pregnancy testing[9]	x_s			x_u			x_u		x_u	x_u	x_u	x_u	x_u	x_u
Gastroscopy[1, 10]		x												
Hepatic venous pressure gradient (HVPG)[1, 11]			x						x				x	
Ultrasound (liver and spleen)[1, 12]		x					x		x				x	x
[redacted]														
Review of in-/exclusion criteria	x	x	x	x										

FLOW CHART contd.

Trial Periods	**Screening[1]**			**Randomised Treatment**										**Follow-Up**
Visit	**1a[1]**	**1b[1]**	**1c[1]**	**2[2]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**EoT / ED[3]**	**EoS[3]**
Week	**-6**			**R**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**
Day	**-42**			**1**	**8**	**15**	**29**	**43**	**57**	**85**	**113**	**141**	**169**	**197**
Time window for visits (days)	**See footnote 1**			**N/A**	**+ 2**	**+ 2**	**+ 2**	**± 3**	**± 3**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**
Fasting status[4]	**NF**	**F**	**F**	**F**	**NF**	**NF**	**F**	**NF**	**F**	**NF**	**NF**	**NF**	**F**	**F**
Randomisation				x										
IRT call				x	x	x	x	x	x	x	x	x	x	
Dispense trial medication				x	x	x	x	x	x	x	x	x		
Dose-titration[14]				x	x	x								
Train patient (home BP and HR monitoring)[15]				x	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	
Home BP and HR monitoring (by patient)[15]				x	→	→	→	→	→	→	→	→	→	→
[redacted]														
Biobanking sampling[19]				x					x				x	
PRO completion (EQ-5D-5L, SF-36v2, CLDQ)[20]				x									x	
All AEs / SAEs / AESIs[21]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Collect trial medication					x	x	x	x	x	x	x	x	x	
Compliance check					x	x	x	x	x	x	x	x	x	
End of trial medication													x	
Completion of patient participation														x

Footnotes:

1. The screening period consists of 3 visits (Visits 1a/b/c). These visits should ideally be completed within a period of 4 weeks, but a maximum of 6 weeks (-42 days) will be permitted. There is no minimum duration. A patient 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. Visit 1b and 1c can be performed on the same day; in that case, the gastroscopy must be performed prior to the HVPG measurement. The ultrasound and [redacted] can be performed at either Visit 1b or 1c. Refer to Sections 5.1.1, 5.1.2, 5.2.5.1, 5.2.5.2 and 6.2.1
2. Visit 2 = randomisation / Day 1 of trial medication. All assessments at this visit (excluding post-dose vital signs and ECGs, [redacted] [refer to Sections 5.2.4, 5.6.1, 6.2 and Appendix 10.1]) should be completed before the first dose of trial medication is administered
3. Patients who complete 24 weeks of treatment will have an End of Treatment (EoT) visit, followed 4 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. Patients 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 4 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 patient has rested for at least 5 minutes in a supine position. From Visit 2 onwards, the patients 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, 7 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 patient 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. Pregnancy testing at dosing visits should be completed prior to administration of trial medication. Refer to Section 5.2.3
10. Refer to Section 5.2.5.2 for details regarding the necessity for a gastroscopy at Visit 1b
11. For further details regarding the HVPG measurement, refer to Section 5.1.1
12. For further details regarding ultrasound of the liver and spleen, refer to Section 5.2.5.1
13. [redacted]
14. For further details regarding dose-titration, refer to Section 4.1.4
15. 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
16. [redacted]
Following training on completion of the diary at Visit 2, subsequent refresher training should be provided if required
17. [redacted]
18. [redacted]
19. 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
20. [redacted]

21. After the EoS visit (= individual patients end of the trial) the Investigator should report only 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 and only via the BI SAE form (refer to Section 5.2.6.2.1)
22. The physical examination at Visit 1a should include an assessment of the clinical criteria for Child-Turcotte-Pugh classification (refer to Appendix 10.3)
23. 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 [redacted]

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ABBREVIATIONS AND DEFINITIONS

A1At	Alpha-1 antitrypsin
AC	Adjudication Committee
[redacted]	
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ANCOVA	Analysis of Covariance
ARLD	Alcohol-Related Liver Disease
AUC	Area Under the concentration-time Curve
BDL	Bile Duct Ligation
BI	Boehringer Ingelheim
BID	*Bis In Die* (twice a day)
BP	Blood Pressure
BPM	Beats Per Minute
CA	Competent Authority
[redacted]	
cGMP	cyclic Guanosine MonoPhosphate
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
[redacted]	
C_{max}	Maximum measured concentration of the analyte in plasma
COVID-19	Coronavirus Disease 19
C_{pre}	Predose concentration of the analyte in plasma
CRA	Clinical Research Associate
CRO	Contract Research Organisation
CSPH	Clinically Significant Portal Hypertension
[redacted]	
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol

CTR	Clinical Trial Report
DBL	Database Lock
DBP	Diastolic Blood Pressure
DDI	Drug-Drug Interaction
DILI	Drug-Induced Liver Injury
DMC	Data Monitoring Committee
DN	Diabetic Nephropathy
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
ED	Early Discontinuation
[redacted]	
EoS	End of Study (corresponds with End of Trial)
EoT	End of Treatment
[redacted]	
ES	Enrolled Set
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAS	Full Analysis Set
[redacted]	
FHVP	Free Hepatic Venous Pressure
Fib-4	Fibrosis-4
GCP	Good Clinical Practice
[redacted]	
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HE	Hepatic Encephalopathy
HERG	Human Ether-a-go-go Related Gene
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
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
LPLT	Last Patient Last Treatment
[redacted]	
MedDRA	Medical Dictionary for Drug Regulatory Activities
MELD	Model for End-stage Liver Disease
[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
[redacted]	
P-gp	Permeability glycoprotein
[redacted]	
PH	Portal Hypertension
[redacted]	
PV	Pharmacovigilance

QD	*Quaque Die* (once a day)
REML	Restricted Maximum Likelihood
REP	Residual Effect Period
RPM	Report Planning Meeting
RS	Randomised Set
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome CoronaVirus 2
SBP	Systolic Blood Pressure
[redacted]	
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]	
TIPS	Transjugular Intra-hepatic Portosystemic Shunt
TGFß	Transforming Growth Factor beta
[redacted]	
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
UGT	Uridine Glucuronyl Transferase
ULN	Upper Limit of Normal
[redacted]	
VCTE	Vibration Controlled Transient Elastography
VH	Variceal Haemorrhage
WHVP	Wedged Hepatic Venous Pressure
(WO)CBP	(Women Of) Child-Bearing 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 approved clinical approaches to prevent PH-related decompensating events in patients with compensated cirrhosis are endoscopic variceal ligations or off-label use of non-selective beta-blockers (NSBBs) or carvedilol for the prophylaxis of a first variceal bleeding. However, not all patients with PH achieve a haemodynamic 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 substantial 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 into 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) and compensated cirrhosis. 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

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).

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

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 (PK) 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] to [redacted]. The single-dose and steady-state PK parameters ($AUC_{0-\infty}$ and $AUC_{0-\tau,ss}$) 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, 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 (C_{max} 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 II program that will recruit patients from Japan and other Asian countries.

Based on the PK analysis of Trial 1366-0004, the exposure to BI 685509 observed in patients with diabetic nephropathy (DN) with an eGFR ranging from 20 – 75 mL/min/1.73 m^2 was comparable 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.

The preliminary population PK model was updated with new data becoming available. The dataset for the population PK model comprised only limited patient data with eGFR between 20 – 30 mL/min/1.73m^2 from Trial 1366-0004. 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] *BID* / [redacted] *BID* / [redacted] *BID*. 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 11-100% higher, and the predicted median $C_{max,ss}$ is 5-26% higher, respectively 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 ~ 2-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/1.73m^2) based on highest titrated dose of [redacted] *ID* at Day 168 / 24 weeks

Measure	eGFR	Median	2.5th	97.5th
$AUC_{0\text{-}24,ss}$	≥ 90	1.00	0.509	2.06
	60 – 90	1.11	0.655	2.31
	45 – 60	1.31	0.691	2.49
	30 – 45	1.63	0.865	3.08
	20 – 30	2.00	1.02	3.87
$C_{max,ss}$	≥ 90	1.00	0.439	1.84
	60 – 90	1.05	0.526	1.94
	45 – 60	1.10	0.464	1.93
	30 – 45	1.20	0.606	2.11
	20 – 30	1.26	0.589	2.27

Source: c35011958

Based on the preliminary PK analysis 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 C_{max} and 729 nmol*h/L $AUC_{0\text{-}tau,ss}$, 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 C_{max} and 604 nmol*h/L $AUC_{0\text{-}tau,ss}$, yielding an estimated total daily exposure of ~1210 nmol*h/L. The exposure observed in the [redacted] *BID* dosing regimen in hepatic impaired patients were comparable to that of the [redacted] *TID* 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 Trial 1366-0004 with eGFR 20 – 75 mL/min/1.73m^2 and in hepatically impaired Child-Turcotte-Pugh A and B patients in Trial 1366-0020. 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 the CSPH indication is close to the clinically relevant dose tested in Phase II. Thus, in addition to close monitoring of AEs among patients taking CYP3A4 narrow therapeutic index / or sensitive substrates, CYP2C8 and CYP3A4 narrow therapeutic index / or sensitive substrates will also be monitored to support patient safety. Inhibitors or inducers 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 pre-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 EC_{50} 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 (n00260803). 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.

Trial 1366-0020, an MRD trial involving hepatically impaired patients, was ongoing during Clinical Trial Protocol (CTP) writing. An interim analysis was performed.

Summary of interim analysis 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.

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.

The exposure was comparable between Child-Turcotte-Pugh A and B patients, and no differences were seen for the different underlying liver aetiologies. Exposure of [redacted] *BID* in hepatic impaired patients were similar to [redacted] *TID* exposures observed in healthy volunteers (Trial 1366-0003) and chronic kidney disease patients (Trial 1366-0004).

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. Spleen stiffness was assessed using the FibroScan® Expert 630 (Echosens), however, due to being a rather new technique, the data generated was inconclusive. [redacted]

Summary of recent data from Trial 1366-0020:
Based on recent data from Trial 1366-0020, an effect of BI 685509 on the predicted placebo-corrected change from baseline QTcF (ΔΔQTcF) was seen. As mentioned above, this trial included patients with cirrhosis Child-Pugh stage A (24 patients) and B (25 patients). Dosing regimens up to [redacted] *BID* (i.e. the same as the highest dose group in this trial) were used. 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 Pugh A) this was concomitant with a change of the predicted placebo-corrected change from baseline heart rate (ΔΔHR) of > 10 beats per minute (bpm), but not in the other patient group. 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.

BI 685509 has no effect on the human ether-a-go-go related gene (hERG) channel at doses used in this clinical trial, and no effect on QT-interval or T-wave morphology was seen in conscious animal studies (for further details refer to the current Investigator's Brochure (IB) [c02778238]).

1.3 RATIONALE FOR PERFORMING THE TRIAL

In this Phase II trial the efficacy of treatment in patients with CSPH (defined by the presence of varices and HVPG ≥ 10 mmHg) in compensated alcohol-related cirrhosis will be assessed. This will be the first trial in the clinical development of BI 685509 where patients will be treated for 24 weeks, and where the portal pressure will be assessed quantitatively via HVPG

measurements. The trial will serve to evaluate both short-term and long-term efficacy. The long-term assessment will be used to rule out any adaptation to sGC activation on portal pressure on chronic treatment. The trial will also provide supportive evidence for the planned Phase III development.

In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking (refer to 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 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 profile of BI 685509 is outlined in the current Investigator's Brochure (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 at an early stage of 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 invasiveness and technical difficulty.

1.4.2 Risks

Trial participants will be exposed to trial-related risks due to exposure to the trial medication, 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 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 1.2.3 and 4.1.2). All patients will be monitored for AEs, and BP and HR will be measured daily (by the patient at home) during the treatment period. Patients with oedema or gastrointestinal side effects will be managed by standard of care, and patients with a known history of orthostatic dysregulation and those with a SBP < 100 mmHg and 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	Patients with long QT / QTcF-interval, patients 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 3.3.4.1).
Risks related to DDI	Refer to Section 1.2.1	Close monitoring of patients 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. Patients 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 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	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, 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)	Risks relating to HVPG measurements will be mitigated by placing the trial at sites who are 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 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)
Possible complications due to gastroscopy include side effects from procedural sedation (e.g. nausea, vomiting, aspiration pneumonia, irregular heartbeat, breathing difficulties), bleeding (e.g. due to damaged blood vessels or ruptured varices) and perforation (e.g. to the oesophageal lining, stomach or duodenum). After the procedure, patients may also experience abdominal bloating / gas caused by the introduction of air into the stomach. These side effects are usually short-lived	A gastroscopy will be performed at screening where required (refer to Section 5.2.5.2). The assessment will allow an assessment of the status of the varices. In general, a gastroscopy is a safe procedure with both a diagnostic and interventional use in liver disease offered to patients with relevant symptoms and for variceal screening and treatment (R21-0296). The risks of serious complications are small	The procedure will be performed by appropriately trained professionals, and sites will be expected to follow local standard processes. Possible risks will be mitigated by monitoring patients for AEs, and patients with contraindications to gastroscopy will be excluded. Patients who develop side effects will be managed according to standard of care

Table 1.4.2: 2 contd. Overview of risks – trial procedures

Possible / known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Ultrasound waves can heat the tissues slightly, and, in some cases, can also produce small pockets of gas in body fluids or tissues (cavitation), the long-term consequences of which are unknown	Ultrasound imaging (sonography) of the liver and spleen will be performed [redacted] primarily to assess the size and depth of the spleen, [redacted] Ultrasound will [redacted] any safety issues such as ascites. It is a safe procedure routinely carried out in patients with liver disease. There are no absolute contraindications to performing an abdominal ultrasound	Ultrasound imaging will be performed by appropriately trained professionals. Risks will be mitigated by monitoring patients for AEs
Potential risks of blood sampling by venepuncture 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
Risks associated with assignment to the placebo treatment group	The placebo control group will control for observer and patient bias, and will enable the evaluation of the absolute effects of BI 685509. The current standard of care for the trial population depends on the presence and size of gastro-oesophageal varices and consists of either monitoring alone or combination treatment with NSBBs or carvedilol and / or endoscopic treatments to prevent bleeding. NSBBs and carvedilol are currently the only available pharmacological therapy of CSPH but not all patients benefit from them (refer to Section 1.1.). The use of a placebo-control group over a 24 week treatment period is considered acceptable, also taking into account the 10- and 20-year survival after development of varices of 42% and 21% respectively for patients with compensated cirrhosis (R20-1200)	This trial will be run on top of current standard of care; stable doses of NSBBs / carvedilol are permitted within the trial (refer to Sections 3.3.2 and 4.2.2.1), and endoscopic variceal ligation is also permitted as required (refer to Section 4.2.1). According to the medication assignment planned, approximately 33% of patients (26) will be randomised to the placebo treatment group

[redacted]

[redacted]

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, 3.3.4.1, 5.2.5.3, 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)
Patients may develop severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or other severe infection	Based on the mode of action BI 685509 is not expected to have a relevant impact on the susceptibility to or the course of an infection. However, the underlying disease(s) of the patient population in this trial and the anticipated age of recruited patients does increase the risk of hospitalisation and intensive care in case of a SARS-CoV-2 or other severe infection	Patients with an active infection with SARS-CoV-2 will be excluded from the trial, and in case of a confirmed severe infection, trial treatment will be discontinued immediately and appropriate measures for monitoring, treatment and quarantine will be implemented. There are no trial-related restrictions regarding COVID-19 vaccination; patients can participate in the trial irrespective of their vaccination status, and vaccination during the trial is not restricted. In the event of force majeure or other disruptive circumstances (e.g. pandemic, war) the investigational plan as per this CTP may not be feasible at a site. With the consent of the patient, the Sponsor and Investigator may agree on alternative, back-up or rescue methodology which may include, but will not be limited to, virtual patient visits and assessments, home healthcare nurse visits, and direct-to-patient shipments of trial medication. For full details refer to Section 6

1.4.3 Discussion

Patients with alcohol-related liver disease (ARLD), cirrhosis, and PH might benefit from the combined anti-fibrotic and anti-portal hypertensive effects of sGC activation (refer to Section 1.1). Treatment with BI 685509 in patients who already developed cirrhosis will potentially

result in the prevention of related complications including decompensation (variceal bleeding, ascites and encephalopathy), transplantation, or liver-related death. The potential risks, as described above, will be minimised by close monitoring of patients, by excluding at-risk patients 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, 5.2.5.3 and 8.7). Hence, overall, in the context of the unmet medical need, the anticipated effects of BI 685509 on CSPH in patients with compensated alcohol-related cirrhosis, and 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 compare two doses of BI 685509 [redacted] and [redacted] *BID*) with placebo, on top of standard of care, in patients with CSPH in compensated alcohol-related cirrhosis. The primary objective is to estimate the mean difference between treatment groups with placebo in percentage change in HVPG from baseline measured after 24 weeks. The primary treatment comparison will be made for treated patients with baseline HVPG measurements (Full Analysis Set, FAS) as if all patients took randomised treatment for the duration of the trial. Safety and tolerability will also be investigated.

2.1.2 Primary endpoint

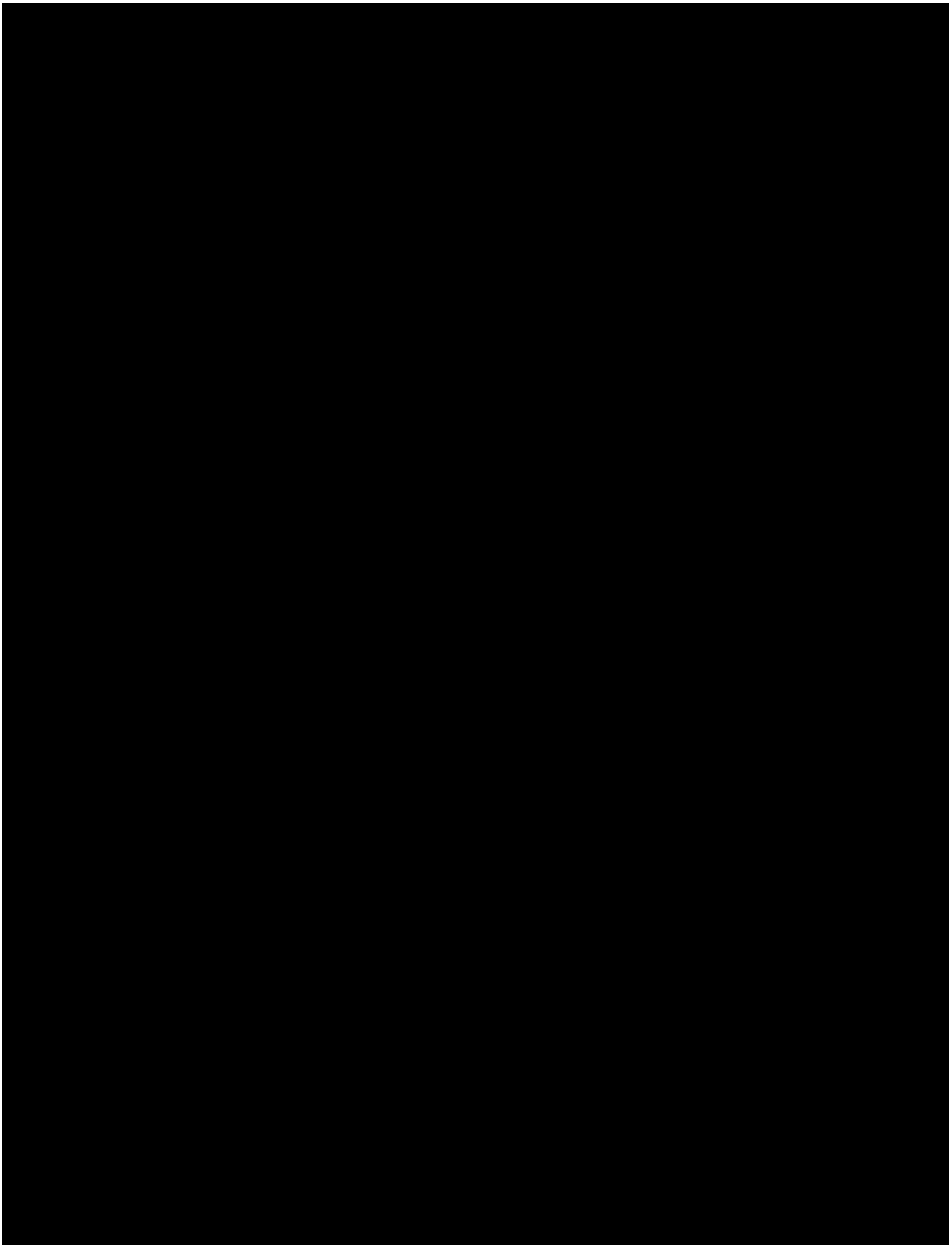
The primary endpoint is the percentage change in HVPG from baseline (measured in mmHg) after 24 weeks of treatment.

2.1.3 Secondary endpoints

Secondary endpoints include:

- percentage change in HVPG from baseline (measured in mmHg) after 8 weeks of treatment
- response defined as > 10% reduction from baseline HVPG (measured in mmHg) after 8 weeks of treatment
- response defined as > 10% reduction from baseline HVPG (measured in mmHg) after 24 weeks of treatment
- occurrence of one or more decompensation events (i.e. ascites, VH, and / or overt HE) during the 24 week treatment period
- occurrence of CTCAE grade 3 (or higher) hypotension or syncope based on Investigator judgement, during the first 8 weeks of the treatment period
- occurrence of CTCAE grade 3 (or higher) hypotension or syncope based on Investigator judgement, during the 24 week treatment period
- occurrence of discontinuation due to hypotension or syncope during the first 8 weeks of the treatment period
- occurrence of discontinuation due to hypotension or syncope during the 24 week treatment period

[redacted]



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This multi-national, placebo-controlled, parallel group trial will compare two doses of BI 685509 [redacted] *BID* and [redacted] *BID*) to placebo, on top of standard of care, in patients with CSPH in compensated alcohol-related cirrhosis. Treatment assignment will be randomised and double-blind.

Patients will be enrolled in the trial and screened for eligibility once they have signed the informed consent. The screening period consists of up to 3 visits (Visits 1a, b and c) and will last a maximum of 6 weeks. Patients will be able to progress from one visit to the next when eligibility of the previous visit is confirmed. Assessments will include a gastroscopy (if applicable – refer to Section 5.2.5.2), ultrasound of the liver and spleen [redacted] and measurement of HVPG. Patients who remain eligible and who successfully complete this period will proceed to the randomised 24 week double-blind treatment period.

In total, 78 patients will be randomised. Randomisation to one of three treatment groups (i.e. one of the two doses of BI 685509 or placebo) will occur at Visit 2 in a 1:1:1 ratio, and it will be stratified by use (or not) of pharmacological treatment of PH (NSBBs / carvedilol).

Following randomisation patients will begin the intake of trial medication and will enter a dose-titration period. All patients in all treatment groups will start this period on a dose of [redacted] *BID* 685509 or matching placebo. If the dose is toler[redacted] one week later (at Visit 3, day 8), the dose for all treatment groups will be up-titrated to [redacted] *BID* 685509 or matching placebo. For the [redacted] *BID* dose treatment group only, and if the dose is tolerated, a second up-titration to [redacted] *D* 685509 or matching placebo will occur after another week (at Visit 4, day 15). However, as this is a double-blind trial, patients randomised both to [redacted] *BID* 685509 and to placebo will also have a dose-titration at Visit 4 (day 15). For these treatment groups the dose-titration will be a pseudo-titration (i.e. those randomised to [redacted] *BID* BI 685509 will remain on that dose, and those randomised to placebo will remain on placebo). Following the dose-titration period, and if the dose is tolerated, patients will remain on their maximum planned maintenance dose for the remainder of the treatment period until they reach the End of Treatment (EoT) visit and 24 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] of the liver and spleen, and the HVPG measurement will be repeated during the randomised treatment period (refer to Figure 3.1: 1).

After approximately 60 randomised patients have completed Visit 7 (week 8 of treatment) and the HVPG procedure, there will be an interim analysis. Recruitment will continue whilst the analysis takes place. The results of the interim analysis will establish short-term efficacy and allow assessment of an internal development milestone. For further details regarding the interim analysis refer to Section 7.2.8.

After the 24 week randomised treatment period all patients will enter a 4 week follow-up period without trial medication. The patient's participation in the trial will be complete when they have performed the last planned visit (i.e. End of Study [EoS], 4 weeks after EoT).

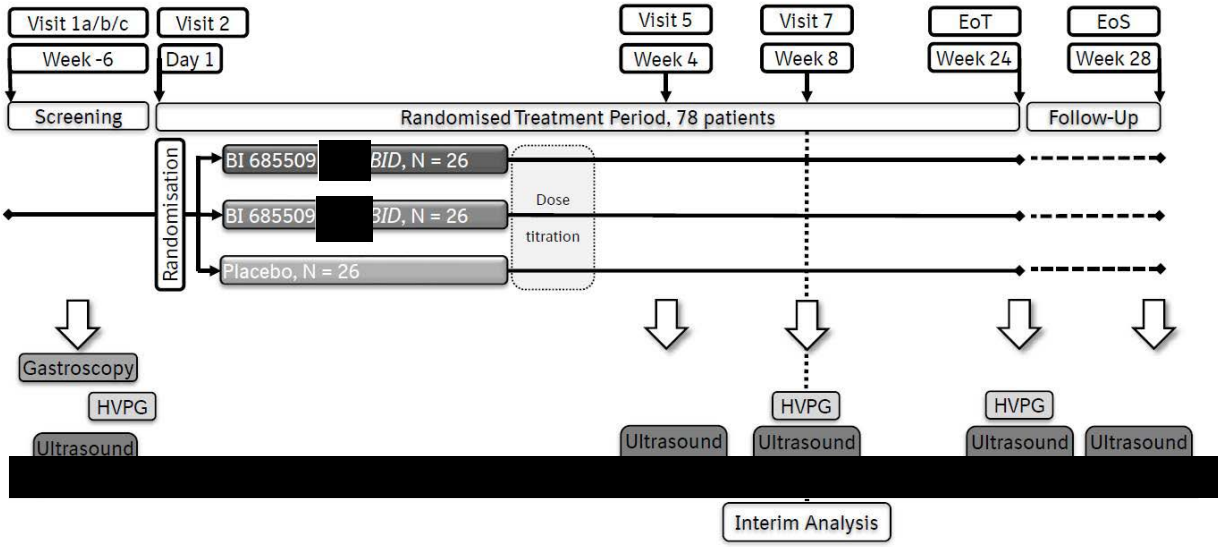


Figure 3.1: 1 Trial design schematic

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

A randomised, double-blind, placebo-controlled and parallel group design has been chosen for this trial, on top of standard of care. The parallel group will enable comparison of three different treatment groups, and the randomised double-blind design will control for assignment bias. For further details regarding the placebo control group refer to Table 1.4.2: 2.

A treatment duration of 24 weeks has been chosen as this should be sufficient to show changes in PH, and hence allow an evaluation of long-term efficacy, and to rule out any adaptation to sGC activation on portal pressure. An interim analysis after 8 weeks of treatment has been included to allow an early evaluation of short-term efficacy (for internal purposes) and to assess a time-dependency of the treatment.

The patient population of this trial has been chosen as it represents a sub-set of the intended patient population for BI 685509. ARLD was chosen as the underlying liver disease based on favourable results from a trial feasibility assessment. The use of NSBBs or carvedilol has been included as a randomisation stratification factor since the use of these concomitant therapies can influence the HVPG lowering effect.

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

The measurement of HVPG was chosen as both the primary, and a secondary endpoint as it is the gold standard to estimate portal venous pressure in patients 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 for 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 one or more 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.

Patients will be screened for the trial based on the eligibility critera (refer to Sections 3.3.2 and 3.3.3). These include the selection of patients with documented endoscopically proven gastro-oesophageal varices, or documented endoscopic-treated oesophageal varices as preventative treatment, as varices only occur in patients with CSPH. At Visit 1c (the final visit within the screening period) patients who remain eligible following Visits 1a and 1b will undergo their first HVPG measurement. Those with an HVPG ≥ 10 mmHg (based on a local interpretation of the pressure tracing) will remain eligible. With this approach, the trial is designed to enrol patients with CSPH but the burden of the invasive HVPG procedure will be reduced and only performed on patients who successfully reach Visit 1c, rather than on all screened patients.

Non-invasive assessments (i.e. ultrasound [redacted] of the liver and spleen and functional liver testing) have been chosen as part of the screening or baseline / Visit 2 procedures to further investigate the patients' status, to establish baseline values for comparison on treatment, [redacted] 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.

Patients selected for this trial have a risk for further progression into decompensation, a severe outcome. A DMC, independent from the Sponsor, will therefore be established to review unblinded 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 blinded 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

78 patients with CSPH in compensated alcohol-related cirrhosis will be randomised into the trial. Approximately 70 sites are planned across multiple countries. It is anticipated that around 2 patients will be randomised at each site. If enrolment is delayed, additional sites may be recruited.

Recruitment of patients for this trial will be competitive, i.e. screening will stop at all sites at the same time once a sufficient number of patients have been screened to deliver the required number of randomised patients. Investigators will be notified about the completion of screening and will not be allowed to screen additional patients thereafter. Patients 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 patient having to be re-screened). This excludes the gastroscopy and the HVPG measurement. Re-screening is also allowed once provided the reasons for screen failure were reversible and have been resolved, based on Investigator judgement. A patient is considered a “re-screener” if he / she was not eligibile for the trial initially and is subsequently re-screened, going through the informed consent process for a second time, receiving a new unique patient number and repeating the screening period assessments.

If, retrospectively, it is found that a patient has been randomised in error (i.e. 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.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF irrespective of whether they have been treated with trial medication or not.

3.3.1 Main diagnosis for trial entry

The trial will include patients in compensated alcohol-related cirrhosis with endoscopic proof of gastro-oesophageal varices, or endoscopic-treated oesophageal varices as preventatitve treatment, as a sign of CSPH, together with an HVPG ≥ 10 mmHg.

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. Clinical signs of CSPH as described by either one of the points below. Each trial patient must have a gastroscopy during the screening period (Visit 1b) or within 6 months prior to screening (Visit 1b). For further details refer to Section 5.2.5.2
   - documented endoscopic proof of oesophageal varices and / or gastric varices at screening (Visit 1b) or within 6 months prior to screening (Visit 1b)
   - documented endoscopic-treated oesophageal varices as preventative treatment

4. CSPH defined as baseline HVPG ≥ 10 mmHg (measured at Visit 1c), based on a local interpretation of the pressure tracing (refer to Section 5.1.1 for further details)

5. Diagnosis of compensated alcohol-related cirrhosis. Diagnosis must be based on histology (historical data is acceptable) or on clinical evidence of cirrhosis (e.g. platelet count < 150 x 10^9/L [150 x 10^3/µL], nodular liver surface on imaging or splenomegaly)

6. 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)

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

8. 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

9. 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

10. 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

[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.

11. 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. Previous clinically significant decompensation events (e.g. ascites [more than perihepatic ascites], VH and / or apparent HE)

2. History of other forms of chronic liver disease (e.g. non-alcoholic steatohepatitis [NASH], Hepatitis B virus [HBV], untreated HCV, autoimmune liver disease, primary biliary cholangitis, primary sclerosing cholangitis, Wilson's disease, haemachromatosis, alpha-1 antitrypsin [A1At] deficiency)

3. Has received curative anti-viral therapy with direct-acting anti-virals within the last 2 years for HCV, or, if such treatment was > 2 years ago and there is no sustained virological response (SVR) at screening (Visit 1a), or, must take curative anti-viral therapy with direct-acting anti-virals throughout the trial (refer to Section 4.2.2.1)

4. ARLD without adequate treatment (e.g. lifestyle modification) or with ongoing pathological drinking behaviour (misuse / abuse based on Investigator judgement)

5. 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

6. SBP < 100 mmHg and DBP < 70 mmHg at screening (Visit 1a)

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

8. Hepatic impairment defined as a Child-Turcotte-Pugh score ≥ B8 at screening (Visit 1a), calculated by the site, using central laboratory results (refer to Appendix 10.3)

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

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

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

12. An active infection with SARS-CoV-2 (or who is known to have a positive test from screening [Visit 1a] until randomisation [Visit 2])

13. Prior orthotopic liver transplantation

14. Prior or planned TIPS or other porto-systemic bypass procedure

15. Known portal vein thrombosis

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

17. 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

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 at screening (Visit 1a) or planned initiation of such therapies during the trial (refer to Section 4.2.2.1)

19. Major surgery (based on Investigator judgement) performed within 3 months prior to randomisation (Visit 2) or planned during the trial, e.g. hip replacement

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

21. 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

22. Any other medical condition[2] that, based on Investigator judgement, poses a safety risk for the patient or may interfere with the objectives of the trial

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

[2]Examples of medical conditions may include, but are not limited to: symptomatic heart failure (New York Heart Association [NYHA] III/IV), known history of tachycardia, clinically relevant arrhythmias, coronary heart disease not compensated by medical treatment (existing unstable angina pectoris)

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 whilst in the trial

3.3.4 Discontinuation of patients from trial medication or assessments

Patients may discontinue trial medication after randomisation, or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; refer to Sections 3.3.4.1 and 3.3.4.2 below. Every effort should be made to keep the patients in the trial, if possible on trial medication. Measures to control the withdrawal rate include careful patient 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 medication after randomisation, or withdraw consent to trial participation, and the reason (if available) must be documented in the patient files and electronic CRF (eCRF). If applicable, consider the requirements for Adverse event collection reporting (refer to Section 5.2.6.2).

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

3.3.4.1 Discontinuation of trial medication

An individual patient will discontinue trial medication if:

- the patient wants to. The patient will be asked to explain the reasons but has the right to refuse to answer
- the patient 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 patient cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future
- the patient needs to take concomitant therapy that interferes with the safety / efficacy of the trial medication (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. Similarly, if a patient needs to modify a dose, where only a stable dose is permitted (e.g. NSBBs / carvedilol, statins), this also will not automatically require discontinuation. In both cases the Sponsor should be consulted
- the patient experiences a severe infection, e.g. with SARS-CoV-2, as determined by the Investigator
- the patient meets the criteria for hepatic injury (refer to Section 5.2.6.1.4 and Appendix 10.2)

- the patient has an acute liver decompensation event such as VH, new-onset of ascites, new-onset of overt encephalopathy, or other new-onset decompensation event based on Investigator judgement
- patients with worsening of their liver function (e.g. from Child-Turcotte-Pugh A to Child-Turcotte-Pugh B with clinical evidence of deteriorating liver function in the opinion of the Investigator). Refer to Child-Turcotte-Pugh classification method in Appendix 10.3
- patients with a QT or QTcF interval > 500 ms, or an increase of QT or QTcF of > 60 ms from the value at Visit 2 / randomisation (baseline). Such cases must be reported as AEs
- the patient can no longer receive trial medication for other medical reasons such as surgery, AEs, other diseases the patient is unblinded by the Investigator (refer to Section 4.1.5.2)
- the patient 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 patient becomes pregnant. The patient will be followed up until birth or otherwise termination of the pregnancy. The data of the patient will be collected and reported in the Clinical Trial Report (CTR) until last patient 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 trial medication 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 patients at any time based on clinical judgement.

If a patient permanently discontinues 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 4 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.

In case of a temporary discontinuation, trial medication 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, BI will review the benefit-risk-assessment and, if needed, pause or discontinue the trial medication for all patients or take any other appropriate action to guarantee the safety of the trial patients.

3.3.4.2 Withdrawal of consent to trial participation

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

If a patient wants to withdraw consent, the Investigator should be involved in the discussion with the patient and explain the difference between trial medication discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial medication discontinuation (refer to Section 3.3.4.1 above). If a patient withdraws consent for further trial participation, no further data will be collected from the respective patient.

3.3.4.3 Discontinuation of the trial by the Sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. New efficacy or safety information invalidating the earlier positive benefit-risk-assessment (e.g. following a recommendation by the DMC). For further details refer to Section 3.3.4.1
3. Deviations from GCP, the CTP, or the contract impairing the appropriate conduct of the trial.

Further treatment and follow up of patients affected will occur as described in Sections 3.3.4.1, 6.2.2.1 and 6.2.3.

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 are BI 685509 and placebo to match BI 685509. BI 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
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	[redacted]
Posology:	*BID*
Method and route of administration:	Oral

Table 4.1.1: 2 BI 685509 [redacted]

Substance:	BI 685509
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	[redacted]
Posology:	*BID*
Method and route of administration:	Oral

Table 4.1.1: 3 BI 685509 [redacted]

Substance:	BI 685509
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	[redacted]
Posology:	*BID*
Method and route 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
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	Not applicable
Posology:	*BID*
Method and route 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
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	Not applicable
Posology:	*BID*
Method and route 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
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	Not applicable
Posology:	*BID*
Method and route 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 multiple oral rising dose trial in patients with DN has 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.

A human dose of [redacted] *BID* is predicted to achieve relevant exposure in patients with hepatic impairment (c02778238, n00261471-01). As [redacted] is the maximum tolerated single

dose, only 2 doses [redacted] *BID* and [redacted] *BID*) will be evaluated in this trial, as measurable differences are not expected between a very low dose and placebo. These doses have been selected based on safety and preliminary PK results from the ongoing Phase I MRD hepatic impairment trial (1366-0020).

4.1.3 Method of assigning patients to treatment groups

After the assessment of all in- and exclusion criteria, each eligible patient will be randomised in a blinded fashion to treatment groups according to a randomisation plan in a 1:1:1 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 patient number (which is generated via the IRT system when a new patient 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 patient

Trial medication will be dispensed at the investigational sites in accordance with the Flow Chart. At dispensing visits patients will be given the appropriate number of medication kits (range 1-4) depending on the interval between the visits (for further kit details refer to Section 4.1.6). The last dose of trial medication will be administered in the evening of the day before the EoT visit.

All patients, 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 patients will either be up-titrated or pseudo 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. Pseudo up-titration will be used at a visit instead of a true up-titration when the maximum planned maintenance dose for a treatment group has been reached; in this way the blind across treatment groups will be maintained (refer to Table 4.1.4: 1). Patients will be informed about the dose titration period and will be made aware that up-titration or pseudo-titration is being used. If a patient 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, patients will continue to receive the maximum planned maintenance dose for the treatment group they are assigned to (unless a down-titration is required), until reaching the EoT visit 24 weeks after starting the trial medication.

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

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

OR

- the dose can be reduced (down-titrated) if the patient 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 and provision of replacement kits, will be managed through the IRT system. Down-titrations must not be performed by instructing the patient 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*) 2 tablets per dose 4 tablets per day	[redacted] **BI 685509** AND [redacted] BI 685509 matching placebo	[redacted] BI 685509 matching placebo AND [redacted] **BI 685509** Up-titration	[redacted] **BI 685509** AND [redacted] BI 685509 matching placebo Pseudo up-titration
Treatment group 2 (BI 685509 [redacted] *BID*) 2 tab er dose 4 tablets per day	[redacted] **BI 685509** AND [redacted] BI 685509 matching placebo	[redacted] BI 685509 matching placebo AND [redacted] **BI 685509** Up-titration	[redacted] BI 685509 matching placebo AND [redacted] **BI 685509** Up-titration
Treatment group 3 (Placebo to BI 685509) 2 tablets per dose 4 tablets per day	[redacted] BI 685509 matching **placebo** AND [redacted] BI 685509 matching **placebo**	[redacted] BI 685509 matching **placebo** AND [redacted] BI 685509 matching **placebo** Pseudo up-titration	[redacted] BI 685509 matching **placebo** AND [redacted] BI 685509 matching **placebo** Pseudo up-titration

From the start of the randomised treatment period (i.e. from Visit 2), and until reaching the EoT visit 24 weeks later, patients will be instructed to take the trial medication orally twice a day (*BID*). Each dose will consist of two film-coated tablets, hence 4 tablets will be taken per day. 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. Doses of the trial medication 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.

On the morning of a visit, the trial medication will be administered as part of the visit. Therefore, on these days, patients should be instructed not to take their morning dose in advance of the visits. [redacted]

Patients 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 patient will self-administer their medication at home. Patients 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 patient visits to sites may not be feasible or may need to be restricted to ensure patient 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 patient's home.

4.1.4.1 Rules for down-titration in case of intolerance to trial medication

If a patient 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 patient has successfully completed the dose titration period (i.e. Visit 4) and is either still taking their assigned dose of trial medication, or if they have missed ≤ 3 consecutive doses[3]. If the patient 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 patient must permanently discontinue treatment (refer to Section 3.3.4.1).

- if the patient is currently receiving either [redacted] *BID* BI 685509 or [redacted] *BID* 685509 (or corresponding matching placebo) the dose will be down-titrated one level i.e.
  - [redacted] *BID* BI 685509 / matching placebo down-titrates to [redacted] *BID* BI 685509 / matching placebo
  - [redacted] *BID* BI 685509 / matching placebo down-titrates to [redacted] *BID* BI 685509 / matching placebo

Once down-titration has taken place, no further up-titration will be permitted.

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

If a patient 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. Depending on the randomisation assignment, this may be a pseudo down-titration i.e.:

- if the patient is currently receiving [redacted] *BID* BI 685509 or matching placebo the dose will be down-titrated to [redacted] *BID* BI 685509 matching placebo (a patient previously down-titrated to [redacted] *BID* BI 685509 matching placebo will be pseudo down-titrated)
- if the patient is currently receiving [redacted] *BID* BI 685509 or matching placebo the dose will be down-titrated to [redacted] *BID* BI 685509 / matching placebo

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). Patients 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 trial medication

An interruption of trial medication may have an influence on the tolerability. Hence, if a patient has missed > 3 consecutive doses[4] 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 patient. 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 patient should re-start the dose titration period at [redacted] *BID* BI 685509 / matching placebo independent of the dose the patient was receiving previously
- before any further up-titration occurs the patient must have taken the preceding dose for at least 7 consecutive days. This applies throughout the treatment period
  - this may mean that a patient 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

Patients 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.

[4]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

Patients, Investigators, central reviewers, and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial (except as noted below) will remain blinded with regard to the randomised treatment assignment until the database is declared ready for analysis according to the Sponsor's SOPs. Further details regarding the time point of unblinding the database for analysis will be documented in the TSAP. One interim analysis will also be performed. For details (e.g. timing, access to unblinded data, and how results will be controlled) refer to Section 7.2.8.

The access to the randomisation code will be kept restricted until its release for analysis.

A DMC, independent from the Sponsor, will perform an unblinded safety evaluation at intervals specified in the DMC charter in order to ensure that patients 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 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 patient is unblinded by the Investigator, the patient 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 patients 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 BI 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 will contain one wallet and each wallet will hold 40 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. Patients 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 patient, and the return to the Sponsor or warehouse / drug distribution centre or alternative disposal of unused medication. If applicable, the Sponsor or warehouse / drug distribution centre 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 patients. The Investigator or designee will maintain records that document adequately that the patients 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 patient 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 patient 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 and NSBBs / carvedilol. 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.

There are no trial-related restrictions regarding COVID-19 vaccination; patients can participate in the trial irrespective of their vaccination status, and vaccination during the trial is also not restricted.

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). These restrictions apply from within 5 half-lives prior to randomisation (Visit 2), until the EoS visit.

- 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)

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

- clinically relevant OATP1B1/3 inhibitors

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

In addition, intake of concomitant therapies with a known risk of Torsade de Pointes must not be co-administered with BI 685509 (also refer to Table 1.4.2: 1). 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.

Furthermore, patients 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 patients 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).

Within the last 2 years, and throughout the entire trial (from screening [Visit 1a] to the EoS visit), treatment of HCV with curative anti-viral therapy with direct-acting anti-virals is also prohibited, since anti-viral therapy may contribute to reduced portal pressure (refer to Section 3.3.3).

4.2.2.1.1 Close monitoring for AEs based on concomitant therapy

If a patient 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 patient (e.g. taking up exercises that put pressure on the abdomen, such as weightlifting).

Alcohol consumption must be avoided throughout the trial; excessive alcohol consumption could lead to hypotension when taken concomitantly with BI 685509. During the treatment period, patients 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 patient may eat as normal.

4.2.2.3 Contraception requirements

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 patient 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 patient's partner.

Alternatively WOCBP and male patients 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 patient. 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

Patients 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.

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

If the number of doses taken is not between 80-120%, site staff will explain to the patient 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 haemodynamic 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 1c will be required for eligibility purposes (refer to Section 3.3.2).

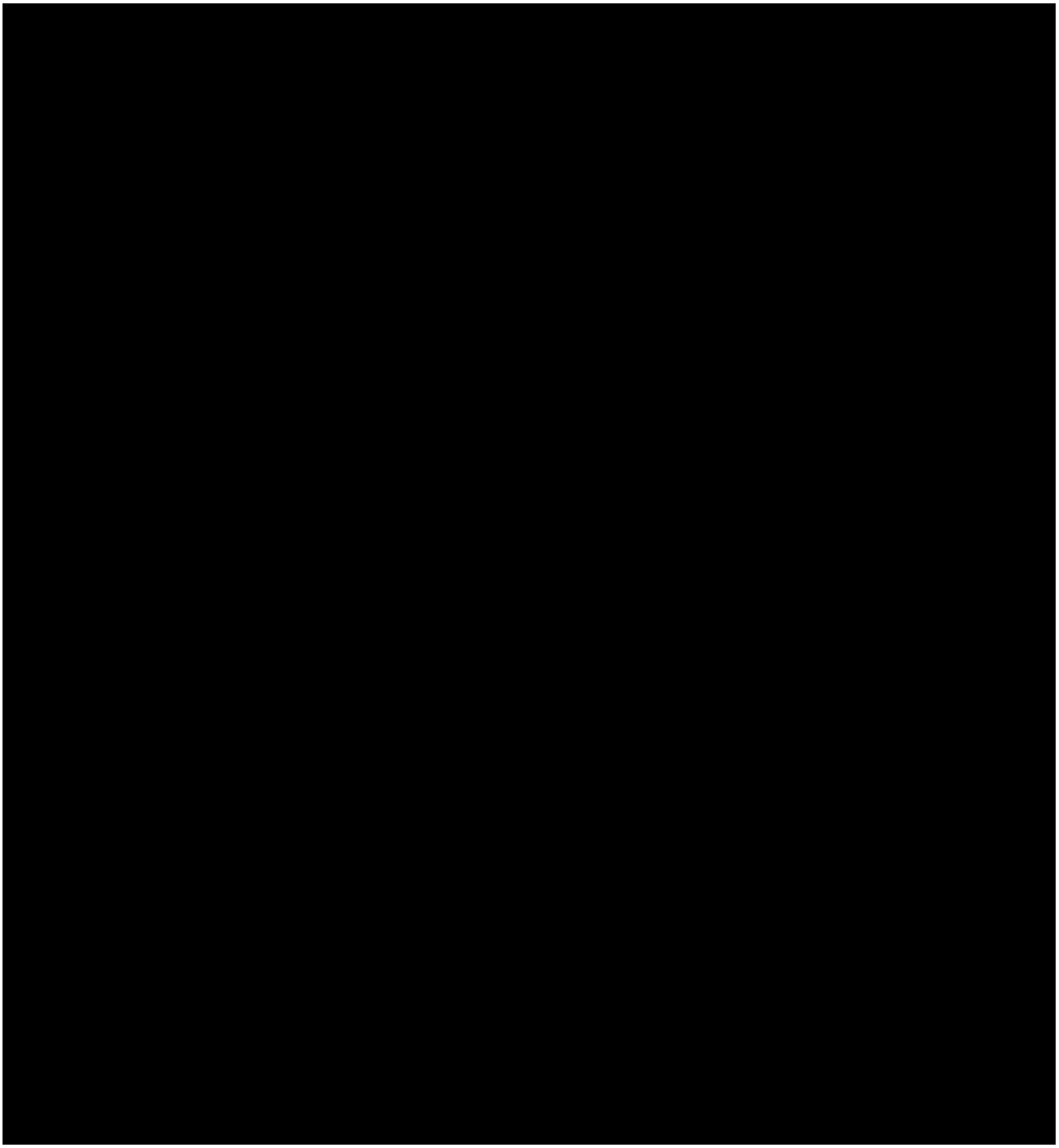
The HVPG procedure within the trial will be conducted in a standardised fashion at all sites (for details refer to the HVPG manual in the ISF); training will be provided. Each trial site will be asked to provide acceptable sample HVPG tracing(s) prior to commencing patient recruitment. Measurements of 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 1c 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 1c 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 1c in the morning an alternative time of day can be chosen; in this case, a fast of at least four hours is required. All subsequent HVPG measurements must then be performed at approximately the same time of day as the Visit 1c measurement for a single patient.

If Visit 1b and 1c are performed on the same day, the HVPG measurement must be performed after the gastroscopy (i.e. only once it is confirmed that the patient remains eligibile for the trial). During the treatment period, following randomisation, HVPG measurements 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 an alternative time of day (i.e. not in the morning, see above) has been chosen for treatment period HVPGs, 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 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination must be performed at the three time points specified in the Flow Chart; further physical examinations are only required if the patient 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 patient. In order to get comparable body weight values, the assessment should be performed in the following way:

- shoes, coat / jackets and any headgear[5] 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 patient's bare midriff, after the patient 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]Headgear worn for religious reasons is acceptable, but this should be worn for all weight measurements in the trial

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 patients 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 patients 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 patient as specified in the Flow Chart. Electronic BP and HR monitoring equipment will be provided for this purpose. Site staff will train the patient 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 patient. Subsequent refresher training should be provided at subsequent visits if required.

Patients will be asked to measure their BP and HR every day in the mornings, 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 patient 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 patient should report these symptoms at the next trial visit. The patient 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.

Patients 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. The fasting status will be recorded for [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 patient not fulfil all laboratory requirements to take part in the trial due to a transitional medical condition, the patient 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 patient (refer to Section 3.3).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (refer to Section 5.2.6.1.4 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 patient 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 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	Haematocrit	HCT
	Haemoglobin	HGB

Category	Test name	Short Name (BI Laboratory Test Code, LBSPID)
	MCV	MCV
	MCH	MCH
	MCHC	MCHC
	RBC count / erythrocytes	RBC
	RBC distribution width (RDW)	RDW
	WBC count / leukocytes	WBC
	Platelet count / thrombocytes	PLTCT
	Reticulocytes	RETABS
Automatic WBC differential (absolute)	Neutrophils	SEGABS
	Eosinophils	EOSABS
	Basophils	BASABS
	Monocytes	MONABS
	Lymphocytes	LYMABS
Coagulation	aPTT	APTTS
	PT	PRTSEC
	INR	INR
	Fibrinogen	FIBR
Clinical chemistry	ALT	SGPT
	Alpha fetoprotein[1]	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[2]	CKMBABS
	eGFR	GFRE
	γ-GT	GGT
	Glucose	GLUB
	LDH	LDH
	Lipase	LIPASE
	Phosphatidylethanol (PEth)[3]	PETH
	Protein (total)	TPRO
	Troponin I[2]	TPONI
	Urea (BUN)	UREA
	Uric acid	URIC
Electrolytes	Bicarbonate	BICARB
	Calcium	CA
	Chloride	CL
	Magnesium	MG
	Phosphate	P
	Potassium	K
	Sodium	NA

Table 5.2.3: 1 contd. Safety laboratory tests

Category	Test name	Short Name (BI Laboratory Test Code, LBSPID)
Lipids[4]	HDL	HDL
	LDL	LDL
	Cholesterol (total)	CHOL
	Triglycerides	TRIGL
Hormones	Aldosterone[5]	ALDOSI
	Renin, plasma[5]	PRCSP
	TSH[6]	TSH
	Free T3[7]	FT3
	Free T4[7]	FT4V
Pregnancy test (serum)	Human Chorionic Gonadotropin[8]	HCG
Pregnancy test (urine)	Human Chorionic Gonadotropin[9]	Not Applicable
Infections screening[6]	HCV antibody (qualitative)	HCAB
	HCV RNA PCR[10]	HCVRNA
	HBV surface antigen (qualitative)	HBSAG
	HBV core antibody (qualitative)	HBCAB
	HBV – DNA[11]	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 Only performed at screening (Visit 1a) and EoT / ED
2 If initial CK is elevated, re-test CK with CK-MB and troponin I
3 Not performed at screening (Visit 1a). PEth, an alcohol-specific biomarker, will be measured during the treatment period for data analysis purposes
4 Not performed at screening (Visit 1a)
5 Not performed at screening (Visit 1a) or Visits 9, 10 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
6 Only performed at screening (Visit 1a)
7 Reflex in case of abnormal TSH
8 WOCBP only; only at Visit 1a, and as a reflex if urine testing is positive
9 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). Pregnancy testing at dosing visits should be completed prior to administration of the trial medication
10 Reflex in case of positive HCV antibody and / or HCV infection that has been treated in the past. Per central laboratory assay, if HCV RNA is < 15 IU / ml at screening (Visit 1a), eligibility criteria are met
11 Reflex in case of positive HBV core antibody and negative HBV surface antigen. Per central laboratory assay, if HBV DNA is < 20 IU / ml at screening (Visit 1a), eligibility criteria are met

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 after the measurement of vital signs, prior to blood sampling and intake of trial medication (at visits where only a single ECG is required), and recorded after the patient has rested for at least 5 minutes in a supine position.

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. [redacted]

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 patient'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 patient 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]

At screening the ultrasound can be performed at either Visit 1b or 1c. 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 (refer to Table 1.4.2: 2). 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, [redacted]

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

5.2.5.2 Gastroscopy

A gastroscopy (i.e an upper gastrointestinal endoscopy) will be performed at the time point specified in the Flow Chart, and after an overnight fast. Details such as the location and size / appearance of varices, the presence / absence of portal hypertensive gastropathy, and the presence / absence of other conditions (e.g. gastritis, duodenitis, ulcers etc.) will be collected in the eCRF.

The gastroscopy can be skipped if the condition below is met. In all other cases, a gastroscopy is required at Visit 1b, and documentary evidence must be available (e.g. source data) following the procedure to confirm the presence of oesophageal / gastric varices.

(i) a patient has had this procedure in the previous 6 months to Visit 1b (and there is documentary evidence [e.g. source data such as a referral letter etc.] available to confirm the presence of oesophageal / gastric varices)

If Visit 1b and 1c are performed on the same day, the gastroscopy must be performed before the HVPG measurement.

Sites will be expected to follow local standard processes when considering the suitability of a patient for the procedure, and whilst conducting the procedure (e.g. use of concomitant therapy and intake of water beforehand, use of procedural sedation etc.).

5.2.5.3 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

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

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

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

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

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

5.2.6.1.2 Serious adverse event

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

- results in death
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe
- requires inpatient hospitalisation 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 patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse

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 Adverse events considered "Always Serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, BI 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 trial medication and must be reported as described in Section 5.2.6.2, sub-sections "AE collection" and "AE reporting to the 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 PV Department within the same timeframe that applies to SAEs; refer to 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 a reasonable possibility of a causal relationship could be:

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

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

- no plausible time to onset of the event relative to the time of trial medication 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 medication concerned)
- continuation of the event despite the withdrawal of the trial medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger
- 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 trial medication concerned
- disappearance of the event even though the trial medication treatment continues or remains unchanged

5.2.6.2 Adverse event collection reporting

5.2.6.2.1 Adverse event collection

The Investigator shall maintain and keep detailed records of all AEs in the patient files.

The following must be collected and documented on the appropriate eCRF(s) by the Investigator:

- from signing the informed consent onwards until the individual patient's end of trial (= the EoS visit): all AEs (serious and non-serious) and all AESIs
- after the individual patient's end of trial: the Investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer and trial medication related SAEs and trial medication related AESIs of which the Investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (refer to Section 5.2.6.2.2), but not on the eCRF

5.2.6.2.2 Adverse event reporting to the Sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form 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. This does not replace the requirement to complete the BI SAE form.

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

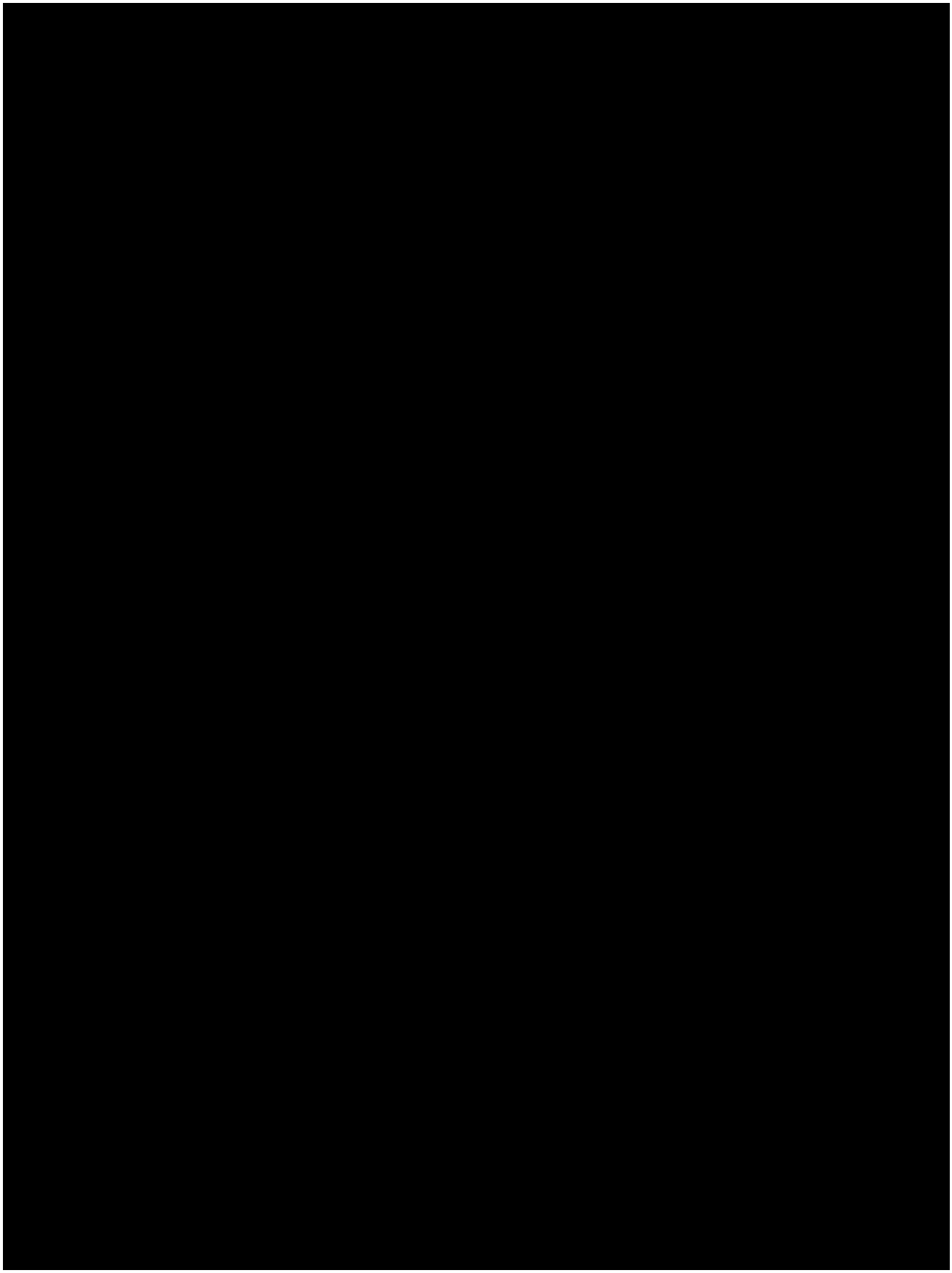
5.2.6.2.3 Pregnancy

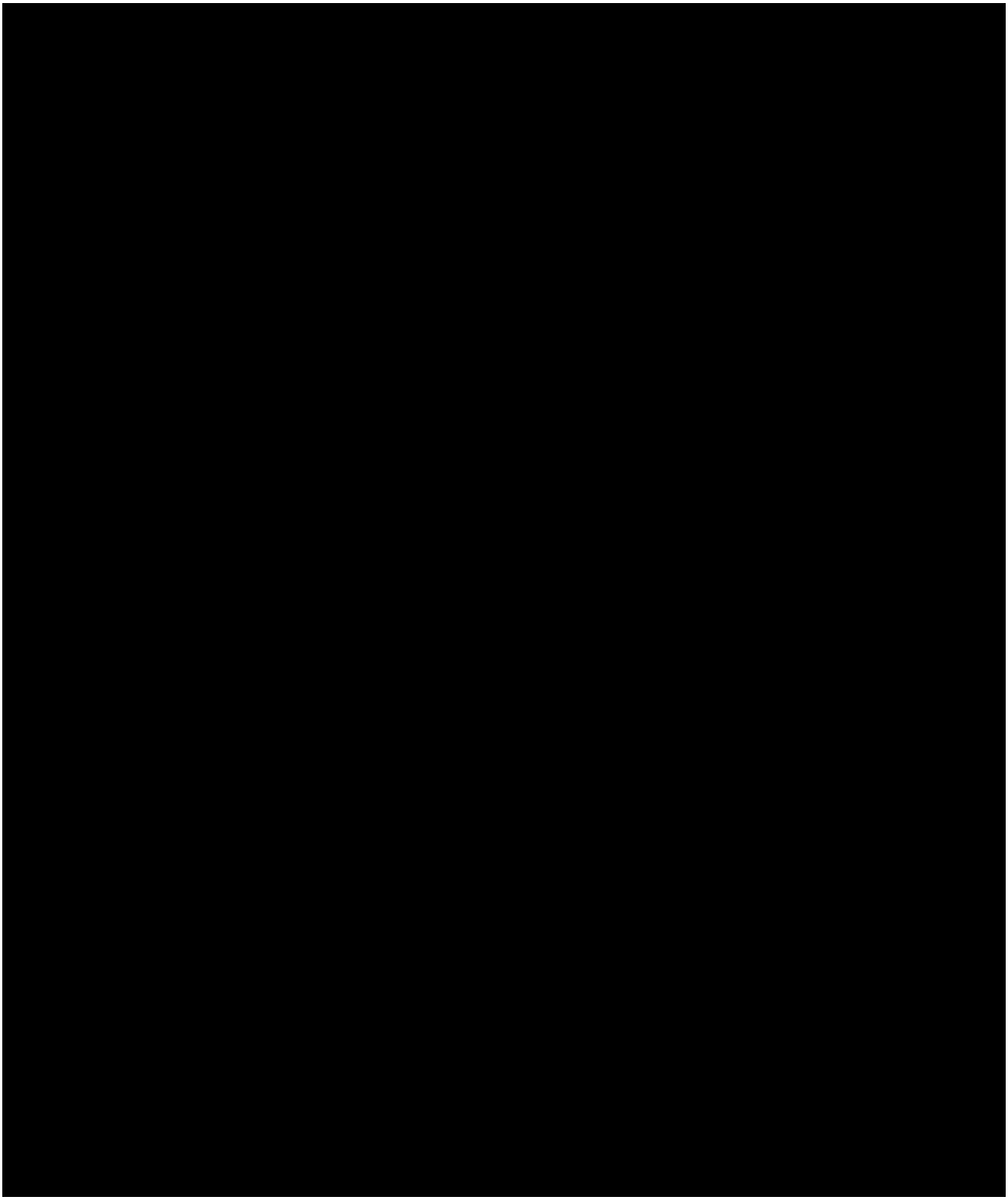
In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the Investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring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

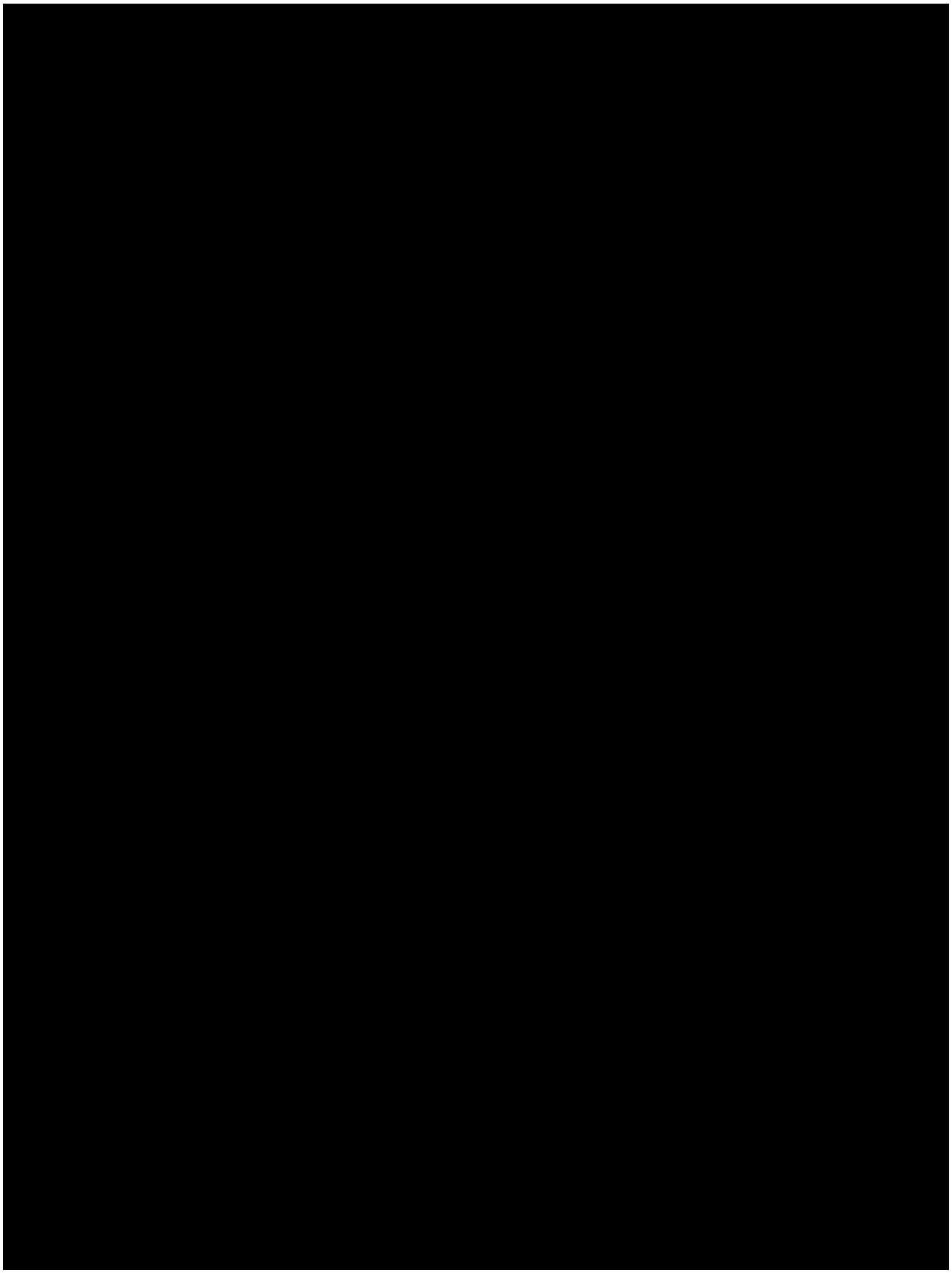
Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner.

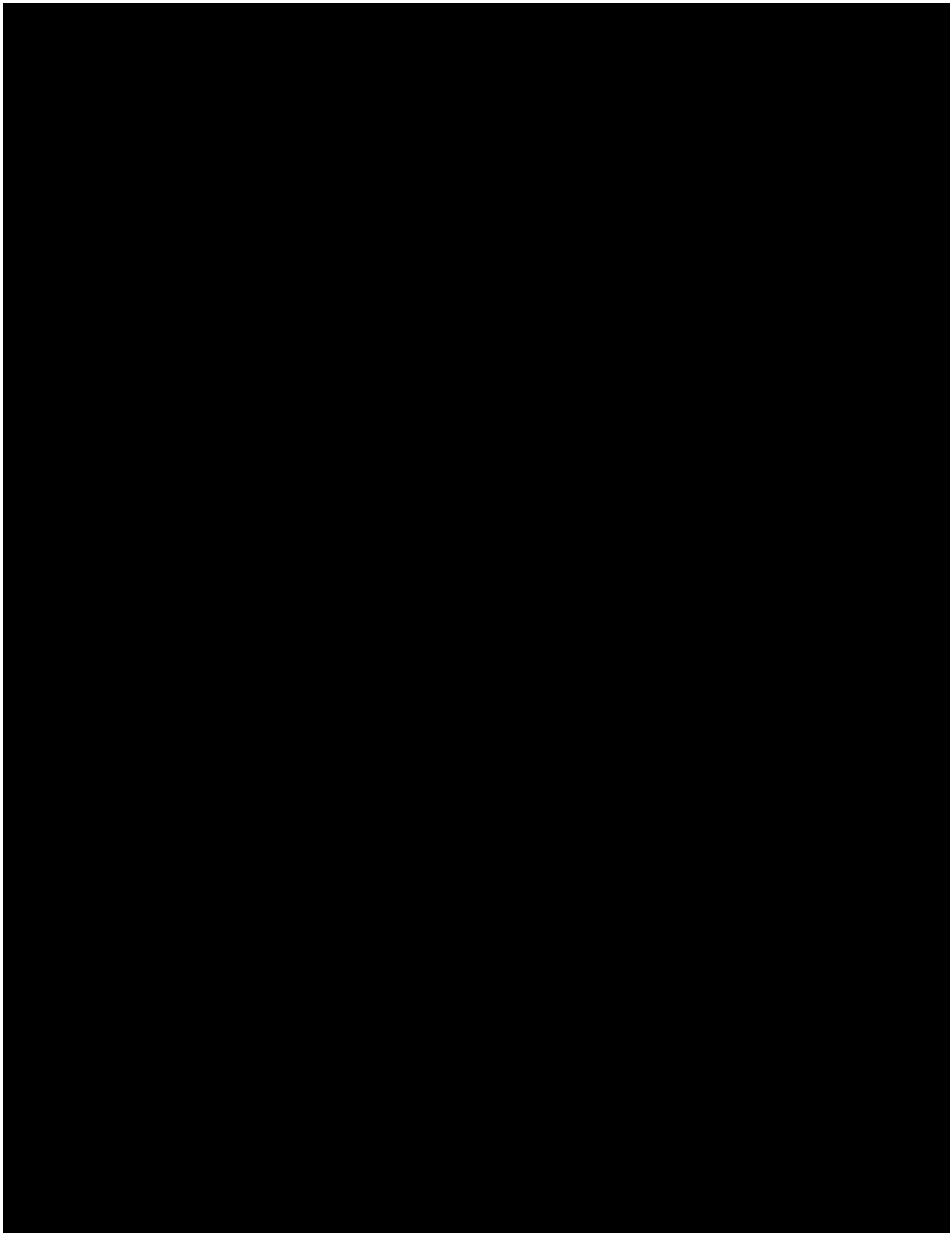
The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the Sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Studies (Part B). The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and B).

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 Clinical Studies and not the SAE form is to be completed. If there is an SAE and / or AESI associated with the pregnancy an SAE form must be completed in addition.









[redacted]

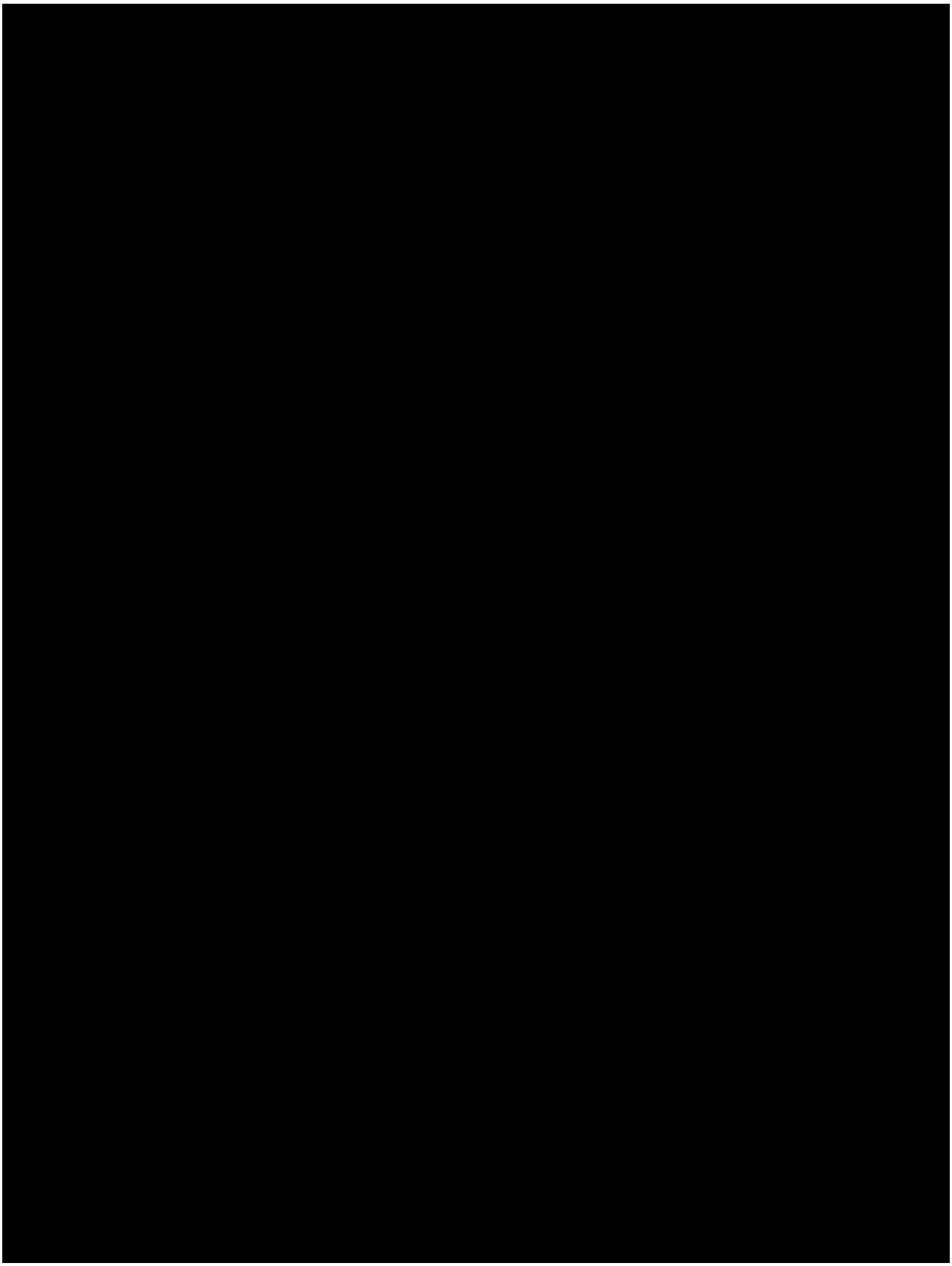
5.5 BIOBANKING

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.

[redacted]



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 investigational plan as per this CTP may not be feasible at a site. With the consent of the patient, the Sponsor and Investigator may agree on alternative, back-up or rescue methodology which may include, but will not be limited to, virtual patient visits and assessments, home healthcare nurse visits, and direct-to-patient shipments of trial medication. Such alternative measures will be mentioned in the patient information, as appropriate. The implementation of these measures will depend on patient'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 randomisation (i.e. Day 1). During the dose titration period of the trial (i.e. from Visit 2 [randomisation] to Visit 4), scheduled trial visits must be at least 7 days apart, since a patient must have taken the preceding dose 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 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, patients should be instructed not to take their morning dose in advance of their clinic visit (refer to Section 4.1.4). [redacted]
status of a patient should be in accordance with the Flow Chart and will be recorded in the eCRF. Patients 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 patient visits to the sites may not be feasible or may need to be restricted to ensure patient safety. Based on a thorough assessment of the benefits and risks, the following visits may be performed at the patient's home, remotely (by phone) or as a combination of home and remote visits:

- Visit 6
- Visit 9

- Visit 10

When scheduling such visits every effort should be made to ensure a continuous supply of trial medication for the patient, whilst also taking into account that the next kit(s) of trial medication may need to be shipped from the site to the patient'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 randomised 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, patients 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).

[redacted]

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

- concomitant therapy
- pregnancy testing (urine)
- IRT call
- dispense trial medication
- train patient / 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 visits performed remotely. Instead, the medication should be collected when the patient next visits the site, or when a visit is performed at the patient's home (see below).

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

- anthropometric measures
- vital signs
- physical examination
- resting 12-lead ECG (using a portable ECG machine)
- safety laboratory sampling and review of results
- collect trial medication

If safety laboratory sampling via the central laboratory is not possible from the investigational site (and is instead performed at the patient'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 (Visits 1a to 1c)

No trial procedures should be performed unless the patient has consented to take part in the trial. Once a patient has consented, he / she is considered to be enrolled in the trial and to have started screening. The patient should be recorded on the enrolment log and be registered in the IRT system as a screened patient. Patients who are not eligible to proceed to Visit 2 (i.e. they fail screening at either Visit 1a, 1b or 1c) 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 3 visits (refer to Flow Chart), namely Visit 1a, Visit 1b and Visit 1c; these visits should ideally be completed within a period of 4 weeks, but a maximum of 6 weeks (-42 days will be permitted prior to randomisation (i.e. Day 1, Visit 2). There is no minimum duration for the screening period. A patient 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. Visit 1b and Visit 1c can be performed as separate visits, or, they can be performed on the same day. If they are performed on the same day, the gastroscopy must be performed prior to the HVPG measurement; in this setting the site can choose whether to perform the ultrasound and [redacted] at Visit 1b or Visit 1c.

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 patient`s sex at birth)
- for female patients: of childbearing potential yes / no in order to characterise the patient population and as a basis for contraception requirements
- ethnicity and race in order to sufficiently characterise the patient 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 patient to be classified as black or non-black (unless not acceptable according to local regulations)

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 patient 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

If a patient is deemed eligible for the trial following Visits 1a, 1b and 1c, the patient 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 patient can be randomised only once into the trial. The randomised treatment period starts with Visit 2 and ends when a patient reaches the EoT visit (refer to the Flow Chart). The last dose of trial medication will be administered in the evening of the day before the EoT visit.

[redacted]

Patients 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 patient must have taken the preceding dose 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]

bring [redacted] and the electronic BP and HR monitoring device with them to each trial visit (refer to Sections 5.2.2.1 and 5.6.2). 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 24 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). 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]
- 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 (End of Study) and trial completion

An EoS visit should be scheduled 4 weeks after an EoT and / or ED visit (refer to the Flow Chart and Section 3.3.4); 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]

Trial completion is defined as a patient who completes 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

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 in comparison to placebo, however it is not planned to test a statistical hypotheses with regard to these variables in a confirmatory sense. 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 patients having signed informed consent and who were eligible for inclusion into the trial. The ES will be used for analyses of patient disposition
- **Randomised set (RS)** – this analysis set includes all enrolled patients 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 patients 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 randomised patients 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 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 / carvedilol concomitant therapy
- occurrence of a decompensation event

All intercurrent events will be handled according to the hypothetical approach as defined in ICH E9 (R1), to perform treatment comparison as if all patients took randomised treatment. Each analysis will reference the strategy for handling intercurrent events that it will be estimating. The estimand for each main analysis in this CTP 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 blinded review and will be documented in the TSAP.

7.2.3 Primary objective analyses

For the primary endpoint (refer to Section 2.1.2), a restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) will be used to obtain adjusted means for the treatment effects. The analysis will include the fixed, categorical effects of treatment at each visit, use of NSBBs or carvedilol (yes / no) at baseline

(refer to Sections 3.1 and 3.2), and the fixed continuous effects of baseline HVPG at each visit. Visit will be treated as the repeated measure with unstructured covariance structure to model the within-patient measurements. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. The analysis will only be used for estimation of treatment effects without performing statistical tests. The analysis will be based on the FAS. Patients 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.

7.2.4 Secondary objective analyses

Unless otherwise stated, only descriptive statistics will be presented for the secondary endpoints defined in Section 2.1.3.

7.2.6 Safety analyses

Safety analyses will be descriptive in nature and follow BI standards, including (but not limited to): AEs, SAEs and AESI. AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All AEs with an onset between start of treatment and end of the REP (refer to Section 1.2.1) will be assigned to the on-treatment period for evaluation.

Safety analyses will be done by “treatment at onset” principle. All treated patients will be included in the safety analysis (TS). 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 AEs will concentrate on treatment-emergent AEs, i.e. all AEs occurring between start of treatment and end of the REP. AEs that start before first trial medication intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of AEs will be tabulated by system organ class and preferred term after coding according to the current version of the MedDRA at DBL.

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 patients 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

An interim anlaysis is planned after the first 60 patients (20 per treatment group) have completed the first 8 weeks of treatment and the HVPG procedure. All available data at this stage will be analysed in the same way as is planned for the final analysis with the only exception of the primary endpoint and one of the secondary endpoints. The primary endpoint will not be analysed since the focus is the week 8 time point for the interim analysis. If applicable, the secondary endpoint defined as "percentage change in HVPG from baseline (measured in mmHg) after 8 weeks of treatment" will be analysed using an analysis of covariance (ANCOVA) model with treatment and baseline HVPG. This model will only be used to estimate treatment effects, no comparison via statistical testing will be performed.

The extent of the safety analyses will be to ensure that the trial is being conducted safely.

The interim analysis will be performed by an independent statistics and programming team within BI. The results of the interim analysis will be used internally and individuals involved in the conduct of the trial will not be made aware of the results. There will be no changes of the design of the trial because of this interim analysis and no stopping rules apply. For this interim analysis an interim analysis SAP and an interim analysis logistics plan will be developed, including a list with individuals and roles who will have access to unblinding information.

An external DMC will be implemented, with tasks and administrative details as briefly 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; the DMC will be informed about the results of the interim analysis.

7.3 HANDLING OF MISSING DATA

[redacted] For the interim analysis, the missing HVPG data at week 8 will not be imputed. For the primary endpoint, the mixed effect model will handle missing data based on a likelihood method under the "missing at random" assumption. No imputation of missing data is planned for the remaining endpoints.

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 the two dose groups of active BI 685509. Patients will be randomised in blocks to one of the three treatment groups in a 1:1:1 ratio. The randomisation will be stratified by use (or not) of NSBBs or carvedilol (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 randomise 78 patients in total in this trial: 26 patients per treatment group (placebo, low dose and high dose of BI 685509) [R21-1984, R21-1945].

In a positive scenario, it was assumed that the mean reduction from baseline HVPG at week 24 would be: 0%, 23%, and 25% for placebo, low, and high dose of BI 685509, respectively (with a standard deviation of 27.5% in each group and a correlation coefficient of 0.2 between the two BI 685509 dose groups). With the sample size of 78 in total (26 per treatment group), there is 94.95% probability to observe a difference of at least 15% points HVPG reduction from baseline between at least one dose group of BI 685509 and placebo. In a negative scenario, this probability is 10.41%, assuming the mean HVPG reduction from baseline would be 0%, 3%, and 4%, respectively (with a standard deviation of 27.5% in each group). Probabilities of achieving an assumed treatment effect within different scenarios are presented in Table 7.5: 1 (R21-1984, R21-1945).

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

Scenario No.	Final analysis (n=26 per treatment group)	
	Assumption of mean reduction in HVPG from baseline to week 24 (BI 685509 [redacted] *BID* / BI 685509 [redacted] *BID* / placebo)	**Probability that the treatment effect[1] is ≥ 15%**
	Positive scenario	
1	23%/21%/0% (SD=27.5%)	91.45%
2	23%/21%/0% (SD=33.0%)	88.62%
3	25%/23%/0% (SD=27.5%)	94.95%
4	25%/23%/0% (SD=33.0%)	92.52%
	Negative scenario	
5	4%/3%/0% (SD=27.5%)	10.41%
6	4%/3%/0% (SD=33.0%)	16.23%

1 Treatment effect defined as difference in mean reduction from baseline to week 24 in HVPG between active treatments and placebo

The calculations were peformed 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 IRB / IEC and 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 patient 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, for fully outsourced trials, documents the rationale and strategies for risk management during trial conduct including monitoring approaches, Supplier 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

eCRFs for individual patients will be provided by the Sponsor. Refer to Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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 **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. 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. gastroscopy, HVPG, ultrasound and [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 eCRF and all source

documents / data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all eCRFs 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 CTP and GCP.

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war; refer to 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 centralised 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 PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the World Health Organisation GCP handbook.

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:

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

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

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

- sample and data usage has to be in accordance with the separate biobanking informed consent
- the BI-internal facilities storing biological samples from clinical trial participants, as well as the external banking facility, are qualified for the storage of biological samples collected in clinical trials
- an appropriate sample and data management system, including audit trail for clinical data and samples to identify and destroy such samples according to the informed consent is in place
- a fit for purpose documentation (ensures compliant usage
-
- samples and / or data may be transferred to third parties and other countries as specified in the biobanking informed consent

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed"). The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial medication (as scheduled per CTP 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 CTP.

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 / CA 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 patients 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 patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by BI.

A Coordinating Investigator will be responsible to coordinate Investigators at the different sites participating in this trial. Tasks and responsibilities will be 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, results of interim analyses, significant safety concerns, and decisions from hepatic injury adjudication for evaluation. While DMC members may be unblinded, measures will be 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. All evaluations will be performed in a blinded fashion.

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 [redacted] 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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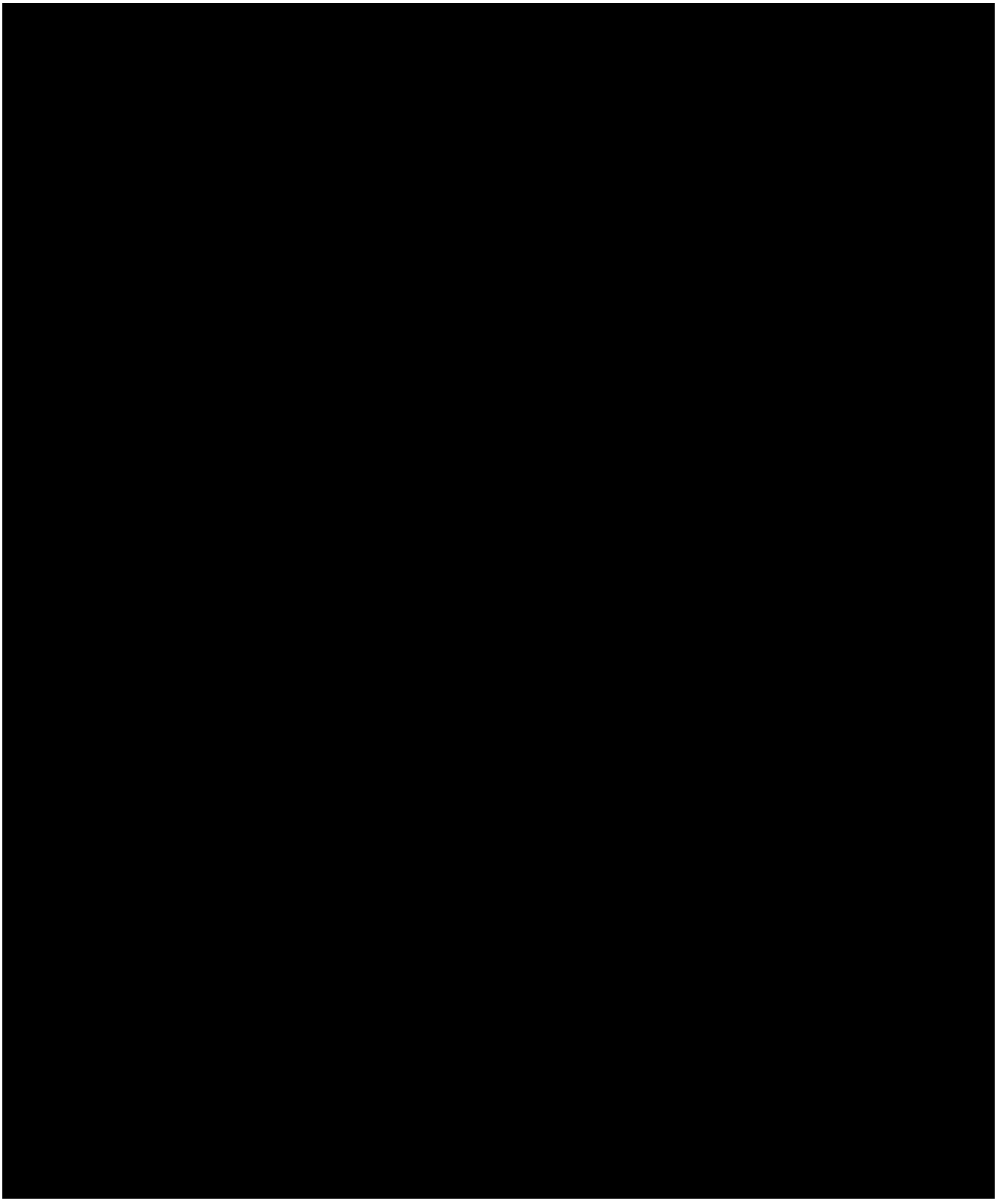
10. APPENDICES



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 randomisation 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

11. DESCRIPTION OF GLOBAL AMENDMENTS

11.1 GLOBAL AMENDMENT 1

Date of Amendment		15 Jul 2021
EudraCT No. **EU Trial No.**		2021-001285-38
BI Trial No.		1366-0021
BI Investigational Medicinal Product		BI 685509
Title of protocol		Randomised, double-blind, placebo-controlled and parallel group trial to investigate the effects of two doses (up-titration to a fixed dose regimen) of oral BI 685509 on portal hypertension after 24 weeks treatment in patients with clinically significant portal hypertension (CSPH) in compensated cirrhosis
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Addition of exclusion criteria to align with adjustment to Section 3.3.3 Exclusion criteria #2 (see below)
Rationale for change		See rationale for Section 3.3.3 EX#2 below
Section to be changed		Abbreviations and Definitions
Description of change		New abbreviation (A1At) added due to addition of exclusion criteria #2 to Section 3.3.3 Exclusion criteria (see below)
Rationale for change		See rationale for Section 3.3.3 EX#2 below
Section to be changed		Section 1.4.2 Risks
Description of change		The last two sentences underneath Table 1.4.2: 2 have been adjusted to align with the adjustment to Section 3.3.3 Exclusion criteria #19 (see below). The text in bold is new. [redacted]
Rationale for change		See rationale for Section 3.3.3 EX#19 below
Section to be changed		Section 3.3.3 Exclusion criteria (EX#2)
Description of change		New exclusion criteria #2 added: “History of other forms of chronic liver disease (e.g. non-alcoholic steatohepatitis [NASH], Hepatitis B virus [HBV], untreated HCV, autoimmune liver disease, primary biliary

		sclerosis, primary sclerosing cholangitis, Wilson's disease, haemachromatosis, alpha-1 antitrypsin [A1At] deficiency)"
Rationale for change		Omitted in error from original protocol. This criteria is required so that the trial population consists only of patients with alcohol-related liver disease
Section to be changed		Section 3.3.3 Exclusion criteria (EX#19)
Description of change		Wording of exclusion criteria #19 adjusted to include the bold text shown below: "Contraindication to any of the trial assessments (e.g. poor patient co-operation for gastroscopy, [redacted]
Rationale for change		

[redacted]

[redacted]		
Section to be changed		Table 7.5: 1 Scenarios of probabilities of achieving the assumed treatment effect
Description of change		Footnote 1 of the table has been adjusted to include the text "Treatment effect defined as combined difference in mean reduction from …." in front of the existing footnote
Rationale for change		Administrative correction
Section to be changed		Section 8.3.1 Source documents
Description of change		The inverted comma has been removed from after the word "trial" in the bullet "completion of patient's participation in the trial …"
Rationale for change		Administrative correction

11.2 GLOBAL AMENDMENT 2

Date of Amendment		21 Sep 2021
EudraCT No. **EU Trial No.**		2021-001285-38
BI Trial No.		1366-0021
BI Investigational Medicinal Product		BI 685509
Title of protocol		Randomised, double-blind, placebo-controlled and parallel group trial to investigate the effects of two doses (up-titration to a fixed dose regimen) of oral BI 685509 on portal hypertension after 24 weeks treatment in patients with clinically significant portal hypertension (CSPH) in compensated cirrhosis
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Flow Chart
Description of change		i) Footnote label 23 added to the rows for vital signs and resting 12-lead ECG ii) Footnote label 22 added to the row for physical examination iii) "x" added to Visits 3, 4, 6 and 8-10 in the row for resting 12-lead ECG iv) Footnote 2 updated with the following bold words "Visit 2 = randomisation / Day 1 of trial medication. All assessments at this visit (excluding post-dose **vital signs and ECGs,** [redacted]

		v) Footnote 3 updated with the following new sentence: "The last dose of trial medication will be administered in the evening of the day before the EoT visit" and the following bold words "… during an ED visit **and the EoS visit that follows it**" vi) Footnote 7 (sentence 1 and 2) updated with the following bold words "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 patient has rested for at least 5 minutes in a supine position.**" vii) Footnote 22 has been added "The physical examination at Visit 1a should include an assessment of the clinical criteria for Child-Turcotte-Pugh classification (refer to Appendix 10.3)" viii) Footnote 23 has been added "During the dose-titration period (i.e. when up-titration is occurring), and at the subsesquent 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 [redacted] (refer to Sections 5.2.2, 5.2.4 and 5.3)"
Rationale for change		i) See rationale for Section 1.2.3 below ii) Clarification iii) See rationale for Section 1.2.3 below iv) See rationale for Section 1.2.3 below v) Clarification vi) See rationale for Section 1.2.3 below vii) Clarification viii) See rationale for Section 1.2.3 below
Section to be changed		Abbreviations and Definitions
Description of change		New abbreviations added for BPM, CI, ECG, HERG BRPM revised to RPM
Rationale for change		To align with other changes made via this global amendment
Section to be changed		1.2.3 Data from clinical studies
Description of change		i) In the first sentence of the third paragraph, the number of patients in Trial 1366-0020 was changed from 48 to 49, and number of patients with cirrhosis Child-Turcotte-Pugh B was changed from 24 to 25

		ii) The following next text has been added to the end of the section: "*Summary of recent data from Trial 1366-0020:* Based on recent data from Trial 1366-0020, an effect of BI 685509 on the predicted placebo-corrected change from baseline QTcF (ΔΔQTcF) was seen. As mentioned above, this trial included patients with cirrhosis Child-Pugh stage A (24 patients) and B (25 patients). Dosing regimens up to [redacted] *BID* (i.e. the same as the highest dose group in this trial) were used. 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 Pugh B) this was concomitant with a change of the predicted placebo-corrected change from baseline heart rate (ΔΔHR) of > 10 beats per minute (bpm), but not in the other patient group. No such effect was seen in healthy Caucasian volunteers for dosing regimens used in Trial 1366-0010. In healthy Asian volunteers (Trial 1366-0013), at a dose regimen relevant for this trial (i.e. starting dose of [redacted] *BID* up to a final dose of [redacted] *BID*), 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. BI 685509 has no effect on the human ether-a-go-go related gene (hERG) channel at doses used in this clinical trial, and no effect on QT-interval or T-wave morphology was seen in conscious animal studies (for further details refer to the current Investigator's Brochure (IB) [c02778238]).".
Rationale for change		i) Administrative correction ii) Based on the change described above, as a precautionary measure, until further investigations about the potential effect of BI 685509 on the QT-interval are conducted, exclusion and discontinuation criteria have been added, as has more frequent ECG monitoring and restricted concomitant therapies have been introduced to protect trial patients from a potential QT-prolongation effect of BI 685509.
Section to be changed		1.3 Rationale for Performing the Trial
Description of change		The words "or genetic" have been removed from the last sentence in this section: "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 AE, or to gain a mechanistic ~~or genetic~~ understanding of drug effects and thereby better match patients with therapies."
Rationale for change		There is no genetic element to the biobanking planned in this trial (biobanking of plasma and serum)
Section to be changed		Table 1.4.2: 1 Overview of risk – investigational medicinal product (BI 685509)
Description of change		New row added to the table for potential QT-interval prolongation, together with a reference to Section 1.2.3 and the following new text for the mitigation strategy: "Patients with long QT / QTcF-interval, patients 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 3.3.4.1)."
Rationale for change		See rationale for Section 1.2.3
Section to be changed		3.3.3 Exclusion criteria
Description of change		i) Wording of EX #3 adjusted to include the bold text shown below: "Has received curative anti-viral therapy with direct-acting anti-virals within the last 2 years for HCV**, or, if such treatment was > 2 years ago** ~~with a~~ **and there is no** sustained virological response (SVR) at screening (Visit 1a)**, or, must take curative anti-viral therapy with direct-acting anti-virals** throughout the trial **(refer to Section 4.2.2.1)**" ii) New EX #18 added: "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 at screening (Visit 1a) or planned initiation of such therapies during the trial (refer to Section 4.2.2.1)"
Rationale for change		i) Criteria re-worded to clarify that patients treated with direct-acting anti-virals > 2 years ago are excluded from the trial if there is no SVR, and that the use of such treatment is prohibited throughout the trial ii) See rationale for Section 1.2.3

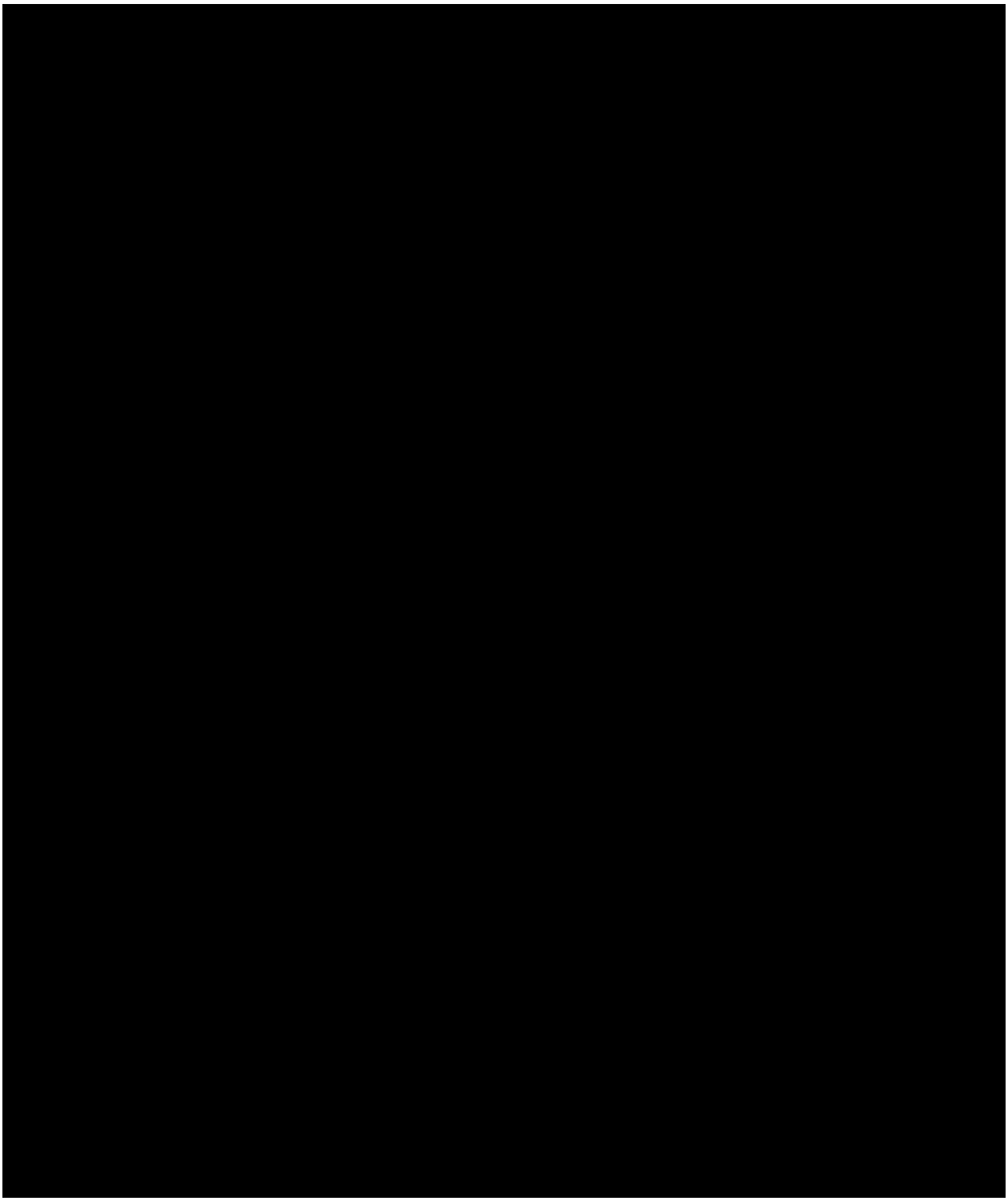
Section to be changed		3.3.4.1 Discontinuation of trial medication
Description of change		New discontinuation criteria added: • "patients with a QT or QTcF interval > 500 ms, or an increase of QT or QTcF of > 60 ms from the value at Visit 2 / randomisation (baseline). Such cases must be reported as AEs"
Rationale for change		See rationale for Section 1.2.3
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		New sentence added at the end of the first paragraph: "The last dose of trial medication will be administered in the evening of the day before the EoT visit."
Rationale for change		Clarification
Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		New paragraph inserted as follows: "In addition, intake of concomitant therapies with a known risk of Torsade de Pointes must not be co-administered with BI 685509 (also refer to Table 1.4.2: 1). 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."
Rationale for change		See rationale for Section 1.2.3
Section to be changed		5.1.1 Hepatic venous pressure gradient
Description of change		2nd paragraph, the word "laboratory" has been deleted from the phrase "HVPG laboratory manual" and the words in bold have been added to the sentence below: "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."
Rationale for change		Clarification

[redacted]

[redacted]

Section to be changed		5.2.2 Vital signs / home blood pressure and heart rate monitoring
Description of change		The words in bold have been added to the sentence below: "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**." The following new sentence has been added to the end of the section: "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)."
Rationale for change		Clarification See rationale for Section 1.2.3
Section to be changed		Table 5.2.3: 1 Safety laboratory tests
Description of change		i) Reticulocytes adjusted so it is a required test rather than reflex in case of anaemia; footnote labels re-numbered as original footnote 1 removed ii) Footnote 10 re-worded to align with re-worded EX #3: "Reflex in case of positive HCV antibody and **/ or** HCV infection **that has been treated in the past**"
Rationale for change		i) To avoid cancellation of reticulocyte results due to short sample stability; a parameter that is important in the trial population ii) See rationale for Section 3.3.3. Exclusion criteria
Section to be changed		5.2.4 Electrocardiogram
Description of change		The words in bold have been added to the sentence below, and two new sentences have been added as a new paragraph: "The 12-lead ECG**s** will be recorded at the time points specified in the Flow Chart; the ECGs should be performed **after the measurement of vital signs,** prior to blood sampling and **intake of trial medication (at visits where only a single ECG is required), and** recorded after the patient has rested for at least 5 minutes in a supine position." "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. [redacted]" The following three sentences have also been added at the end of the section: "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 patient 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."
Rationale for change		See rationale for Section 1.2.3
Section to be changed		6.2 Details of Trial Procedures at Selected Visits
Description of change		The words in bold have been added to the two sentences below: "Exceptions to this are post-dose **vital signs and ECGs,** [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)." A new bullet point has been added to the list of assessments that can be performed at the patient's home: • "resting 12-lead ECG (using a portable ECG machine)"
Rationale for change		See rationale for Section 1.2.3
Section to be changed		6.2.2 Treatment period
Description of change		The words in bold have been added to the sentence below: "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] The following new sentence has been added at the end of paragraph 1: "The last dose of trial medication will be administered in the evening of the day before the EoT visit."
Rationale for change		See rationale for Section 1.2.3 Clarification
[redacted]		



11.3 GLOBAL AMENDMENT 3

Date of Amendment		07 Jul 2022
EudraCT No. **EU Trial No.**		2021-001285-38
BI Trial No.		1366-0021

BI Investigational Medicinal Product		BI 685509
Title of protocol		Randomised, double-blind, placebo-controlled and parallel group trial to investigate the effects of two doses (up-titration to a fixed dose regimen) of oral BI 685509 on portal hypertension after 24 weeks treatment in patients with clinically significant portal hypertension (CSPH) in compensated cirrhosis
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		1.2.1 Key characteristics of BI 685509
Description of change		Drug interaction section: added a potential of a drug-drug interaction with CYP2C8 substrates
Rationale for change		Updated information based on the current version of the BI 685509 Investigator's Brochure
Section to be changed		1.2.3 Data from clinical studies
Description of change		Summary of recent data from 1366-0020 section: correction of a typographical error in the patient group, trial number, and dosing regimen. Information updated about Trials 1366-0003 and 1366-0013
Rationale for change		Correction and clarification
Section to be changed		1.4.2: 1 Overview of risks – investigational medicinal product (BI 685509)
Description of change		In the row "Risks related to DDI", risk updated to include CYP2C8 substrates
Rationale for change		See rationale for Section 1.2.1
Section to be changed		4.2.2.1.1 Close monitoring for AEs based on concomitant therapy
Description of change		Updated to include close monitoring for AEs based on concomitant therapy that is metabolised by CYP2C8
Rationale for change		See rationale for Section 1.2.1
Section to be changed		7.3 Handling of Missing Data
Description of change		Update of the imputation method for different analyses
Rationale for change		To clarify the imputation strategies for missing data

11.4 GLOBAL AMENDMENT 4

Date of Amendment		16 Aug 2022
EudraCT No.		2021-001285-38

EU Trial No.		
BI Trial No.		1366-0021
BI Investigational Medicinal Product		BI 685509
Title of protocol		Randomised, double-blind, placebo-controlled and parallel group trial to investigate the effects of two doses (up-titration to a fixed dose regimen) of oral BI 685509 on portal hypertension after 24 weeks treatment in patients with clinically significant portal hypertension (CSPH) in compensated cirrhosis
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Adjustment to one inclusion criteria and one exclusion criteria to align with adjustments to Sections 3.3.2 Inclusion criteria #6 and 3.3.3 Exclusion criteria #4 (see below)
Rationale for change		See rationale for Sections 3.3.2 IN#6 and 3.3.3 EX#4 below
Section to be changed		Section 3.3.2 Inclusion criteria
Description of change		Wording of inclusion criteria #6 adjusted to include the bold and strikethrough text shown below: "Abstinence from **significant** alcohol **misuse / abuse** for a minimum of **2~~6~~** months prior to screening (Visit 1a), **and the ability** ~~which, based on Investigator judgement,~~ **to abstain from alcohol** ~~can be maintained~~ throughout the trial **(both evaluated based on Investigator judgement**)"
Rationale for change		Based on recruitment difficulties experienced by initiated sites, the requirement for complete abstinence from alcohol prior to the first trial visit has been changed to allow screening of patients without any <u>significant</u> alcohol misuse / abuse (in the opinion of the Investigator). The timeframe has also been reduced from 6 months to 2 months. Patients will still be expected to abstain from alcohol during the trial as previously defined in Section 4.2.2.2 since excessive alcohol consumption could lead to hypotension when taken concomitantly with BI 685509.
Section to be changed		Section 3.3.3 Exclusion criteria
Description of change		Wording of exclusion criteria #4 adjusted to include the bold text shown below: "ARLD without adequate treatment (e.g. lifestyle modification) or with ongoing pathological drinking behaviour **(misuse / abuse based on Investigator judgement)**"

Rationale for change		To align with the change described for Section 3.3.2 Inclusion criteria above.
Section to be changed		Section 11.3 Global Amendment 3
Description of change		In the rows describing changes for Sections 1.4. 2: 1 and 4.2.2.1.1, the words "See rationale for Section 1.2.3" was changed to "See rationale for Section 1.2.1"
Rationale for change		Correction (and described in Protocol Administrative Letter of 13-Jul-22)

11.5 GLOBAL AMENDMENT 5

Date of Amendment		14 Dec 2022
EudraCT No. **EU Trial No.**		2021-001285-38
BI Trial No.		1366-0021
BI Investigational Medicinal Product		BI 685509
Title of protocol		Randomised, double-blind, placebo-controlled and parallel group trial to investigate the effects of two doses (up-titration to a fixed dose regimen) of oral BI 685509 on portal hypertension after 24 weeks treatment in patients with clinically significant portal hypertension (CSPH) in compensated cirrhosis
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Adjustment to total number of patients randomised, number of patients per treatment group and two inclusion criteria to align with adjustments elsewhere in this global amendment (see below)
Rationale for change		See rationale for Sections 7.5 and 3.3.2
Section to be changed		Flow Chart
Description of change		i) "Week" and "Day" adjusted for screening period ii) Time window for screening period removed and replaced with a reference to footnote 1 iii) Footnote 1 adjusted with the bold and strikethrough text shown below: "The screening period consists of 3 visits (Visits 1a/b/c). These visits should **ideally** be completed within **a period of 4 weeks, but a** maximum ~~3-4~~ **of 6** weeks (~~-28~~**42** days~~, window~~

		~~+ 7 days, range -21 to -28~~) **will be permitted**. There is no minimum duration. A patient can ….."
Rationale for change		To assist sites with scheduling difficulties for the required screening assessments, the permitted duration of the screening period has been increased by 2 weeks
Section to be changed		Abbreviations and Definitions
Description of change		New abbreviation added for SSc
Rationale for change		To align with other changes made via this global amendment
Section to be changed		Section 1.2 Drug Profile
Description of change		Systemic sclerosis (SSc) added as a third intended indication for BI 685509
Rationale for change		Updated information based on the current version of the BI 685509 Investigator's Brochure
Section to be changed		Table 1.4.2: 2 Overview of risks - procedures
Description of change		In the row "Risks associated with assignment to the placebo group", the mitigation strategy has been adjusted (from 50 to 35) with the number of randomised patients who will be assigned to the placebo treatment group
Rationale for change		To align with other changes made via this global amendment
Section to be changed		Section 3.1 Overall Trial Design
Description of change		i) Screening period duration adjusted from 4 to 6 weeks ii) Total number of patients randomised adjusted from 150 to 105
Rationale for change		i) See rationale for Flow Chart above ii) See rationale for Section 7.5 Determination of Sample Size below
Section to be changed		Figure 3.1: 1 Trial Design Schematic
Description of change		i) Screening period during adjusted from 4 to 6 weeks ii) Total number of patients randomised adjusted from 150 to 105, and number of patients per treatment group adjusted from 50 to 35
Rationale for change		i) See rationale for Flow Chart above ii) See rationale for Section 7.5 Determination of Sample Size below
Section to be changed		Section 3.3 Selection of Trial Population
Description of change		i) Total number of patients randomised adjusted from 150 to 105 ii) Number of patients anticipated to be randomised at each site adjusted from 2-3 to 2

Rationale for change		i) See rationale for Section 7.5 Determination of Sample Size below ii) To align with other changes made via this global amendment
Section to be changed		Section 3.3.2 Inclusion criteria
Description of change		i) Wording of inclusion criteria #3 adjusted to include the bold and strikethrough text shown below: "Clinical signs of CSPH as described by either one of the points below. Each trial patient must have a gastroscopy during the screening period (Visit 1b) or within ~~3~~**6** months prior to screening (Visit 1b). For further details refer to Section 5.2.5.2 • documented endoscopic proof of oesophageal varices and / or gastric varices at screening (Visit 1b) or within ~~3~~**6** months prior to screening (Visit 1b) • documented endoscopic-treated oesophageal varices as preventative treatment" ii) Wording of inclusion criteria #9 adjusted to include the bold and strikethrough text shown below: "If receiving treatment with NSBBs or carvedilol must be on a stable dose for at least ~~3~~**1** month~~s~~ prior to screening (Visit 1b), with no planned dose change throughout the trial"
Rationale for change		i) To ease recruitment difficulties by permitting the use of a historical gastroscopy over a longer period of time prior to screening, due to the invasive nature of this procedure ii) To ease recruitment difficulties by reducing the amount of time that a stable dose of NSBBs or carvedilol is required prior to screening
Section to be changed		Section 4.2.2.1 Restrictions regarding concomitant treatment
Description of change		4th paragraph adjusted to align with other changes made via this global amendment in relation to the stability of NSBBs or carvedilol prior to screening
Rationale for change		See rationale for Section 3.3.2
Section to be changed		Section 5.1.1 Hepatic venous pressure gradient
Description of change		The following sentence has been added to the 4th paragraph: "If an alternative time of day (i.e. not in the morning, see above) has been chosen for treatment period HVPGs, the morning dose of trial medication can be taken prior to the procedure."
Rationale for change		Clarification

[redacted]		
Section to be changed		Section 5.2.5.1 Ultrasound (liver and spleen)
Description of change		[redacted] ii) The words "at screening (Visit 1b or 1c)" have been removed from the last sentence of the penultimate paragraph
Rationale for change		[redacted] ii) Correction, since the liver and spleen parameters mentioned are measured each time an ultrasound is performed, and not just at the screening visit
Section to be changed		Section 5.2.5.2 Gastroscopy
Description of change		i) Wording adjusted in the 2nd paragraph with the bold and strikethrough text shown below: "The gastroscopy can be skipped if ~~both of~~ the condition~~s~~ below ~~are~~**is** met. In all other cases, a gastroscopy is required at Visit 1b, and documentary evidence must be available (e.g. source data) following the procedure to confirm the presence of oesophageal / gastric varices. (i) a patient has had this procedure in the previous ~~3~~**6** months to Visit 1b (and there is documentary evidence [e.g. source data such as a referral letter etc.] available to confirm the presence of oesophageal / gastric varices) ~~(ii) there has been no change in the treatment of the PH since the gastroscopy was performed (i.e. the "treatment" has been monitoring alone)[6]~~" ii) Footnote 6 has been deleted
Rationale for change		i) See rationale for Section 3.3.2 ii) To ease recruitment difficulties, if therapy with NSBBs / carvedilol was initiated after a historical gastroscopy, the requirement for a further gastroscopy to confirm the persistence of varices has been removed
Section to be changed		Section 6.2.1 Screening period (Visits 1a to 1c)

Description of change		Wording adjusted for the screening period duration and permitted time window to reflect adjustments to the Flow Chart
Rationale for change		To align with other changes made via this global amendment (see rationale for Flow Chart)
Section to be changed		Section 7.5 Determination of Sample Size
Description of change		Total number of patients updated to 105 with 35 patients per treatment group, and the corresponding probabilities of achieving the assumed treatment effects (a difference of at least 20% points HVPG reduction from baseline between at least one dose group of BI 685509 and placebo) in the final analysis were updated. The correlation coefficient of the mean reduction of HVPG from baseline at week 24 in two BI 685509 dose groups was added.
Rationale for change		To increase the trial efficiency while preserving the probability to observe a difference of at least 20% points HVPG reduction from baseline between at least one dose group of BI 685509 and placebo under a positive scenario.

11.6 GLOBAL AMENDMENT 6

Date of Amendment		02 Nov 2023
EudraCT No. **EU Trial No.**		2021-001285-38
BI Trial No.		1366-0021
BI Investigational Medicinal Product		BI 685509
Title of protocol		Randomised, double-blind, placebo-controlled and parallel group trial to investigate the effects of two doses (up-titration to a fixed dose regimen) of oral BI 685509 on portal hypertension after 24 weeks treatment in patients with clinically significant portal hypertension (CSPH) in compensated cirrhosis
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		i. Adjustment to total number of patients randomised and the corresponding number of patients per treatment group ii. Main exclusion criteria: “primary biliary sclerosis” replaced by “primary biliary **cholangitis**”
Rationale for change		i. See rationale for Section 7.5 Determination of Sample Size below ii. Correction / clarification

Section to be changed		Table 1.4.2: 2 Overview of risks - procedures
Description of change		In the row "Risks associated with assignment to the placebo group", the mitigation strategy has been adjusted (from 35 to 26) with the number of randomised patients who will be assigned to the placebo treatment group
Rationale for change		To align with other changes made via this global amendment
Section to be changed		Section 3.1 Overall Trial Design
Description of change		Total number of patients randomised adjusted from 105 to 78
Rationale for change		See rationale for Section 7.5 Determination of Sample Size below
Section to be changed		Figure 3.1: 1 Trial Design Schematic
Description of change		Total number of patients randomised adjusted from 105 to 78, and number of patients per treatment group adjusted from 35 to 26
Rationale for change		See rationale for Section 7.5 Determination of Sample Size below
Section to be changed		Section 3.3 Selection of Trial Population
Description of change		Total number of patients randomised adjusted from 105 to 78
Rationale for change		See rationale for Section 7.5 Determination of Sample Size below
Section to be changed		Section 3.3.3 Exclusion criteria
Description of change		Exclusion criteria no. 2 adjusted as shown below: 2. History of other forms of chronic liver disease (e.g. non-alcoholic steatohepatitis [NASH], Hepatitis B virus [HBV], untreated HCV, autoimmune liver disease, primary biliary ~~sclerosis~~**cholangitis**, primary sclerosing cholangitis, Wilson's disease, haemachromatosis, alpha-1 antitrypsin [A1At] deficiency)
Rationale for change		Refer to rationale for Clinical Trial Protocol Synopsis
Section to be changed		Table 5.2.3: 1 Safety laboratory tests
Description of change		The text in bold has been added to footnotes 10 and 11: **10** Reflex in case of positive HCV antibody and / or HCV infection that has been treated in the past. **Per central laboratory assay, if HCV RNA is < 15 IU / ml at screening (Visit 1a), eligibility criteria are met** 11 Reflex in case of positive HBV core antibody and negative HBV surface antigen. **Per central laboratory assay, if HBV DNA is < 20 IU / ml at screening (Visit 1a), eligibility criteria are met**

Rationale for change		Clarification for interpretation of HCV RNA and HBV DNA reflex results
Section to be changed		Section 7.5 Determination of Sample Size
Description of change		Total number of patients updated to 78 with 26 patients per treatment group, and the corresponding probabilities of achieving the assumed treatment effects (a difference of at least 15% points HVPG reduction from baseline between at least one dose group of BI 685509 and placebo) in the final analysis were updated. Software version for calculations also updated.
Rationale for change		A smaller sample size is required to observe a difference of at least 15% points HVPG reduction from baseline between at least one dose group of BI 685509 and placebo under a positive scenario. 20% HVPG reduction was chosen due to academic guidelines on clinical development for portal hypertension at start of development in 2018. More recent data has shown, that already a 10% reduction of portal pressure has a positive effect on outcomes (R20-1204, R23-3868, R20-3280), therefore, it was decided to reduce the threshold to 15% HVPG reduction.
Section to be changed		Section 9.1 Published References
Description of change		Two references added as shown below: R20-3280 Abraldes JG, Garcia-Tsao G. The design of clinical trials in portal hypertension. Semin Liver Dis; 2017;37(1);73-84. R23-3868 Villanueva C, Aracil C, Colomo A, Hernandez-Gea V, Lopez-Balaguer JM, Alvarez-Urturi C, et al. Acute hemodynamic response to beta-blockers and prediction of long-term outcome in primary prophylaxis of variceal bleeding. Gastroenterology 2009;137(1):119-128
Rationale for change		References added in support of the “rationale for the change” provided above for Section 7.5.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader	[redacted]	02 Nov 2023 16:03 CET
Approval-Team Member Medicine		02 Nov 2023 16:21 CET
Approval-Biostatistics		03 Nov 2023 03:22 CET
Verification-Paper Signature Completion		06 Nov 2023 08:37 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**