TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c44538732-01**
BI Trial No.:	**1366-0029**
Title:	Randomised, open label and parallel group trial to investigate the effects of oral BI 685509 alone or in combination with empagliflozin on portal hypertension after 8 weeks treatment in patients with clinically significant portal hypertension (CSPH) in compensated cirrhosis Including Protocol Revision 6 [include c36380139-06]
Investigational Product(s):	Avenciguat and empagliflozin
Responsible trial statistician(s):	[redacted] Tel.: [redacted]
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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALQ	Above Limit of Quantification
ALT	Alanine transaminase
ANCOVA	Analysis of Covariance
AST	Aspartate transaminase
ATC	Anatomical-Therapeutic-Chemical classification
BI	Boehringer Ingelheim
BIcMQ	BI-customised MedDRA query
BLQ	Below Limit of Quantification
BMI	Body mass index
CI	Confidence Interval
CTCAE	Common Terminology Criteria for Adverse Events
CTR	Clinical Trial Report
DBL	Database Lock
DBLM	Database Lock Meeting
DILI	Drug-Induced Liver Injury
DMC	Data Monitoring Committee
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EoS	End of Study (corresponds with End of Trial)
EoT	End of Treatment
FAS	Full Analysis Set
FAST™	FibroScan-AST
Fib-4	Fibrosis-4
HVPG	Hepatic Venous Pressure Gradient
WHVP	Wedged Hepatic Venous Pressure
FHVP	Free Hepatic Venous Pressure
PFHVP	Proximal Free Hepatic Venous Pressure
ICH	International Council on Harmonisation

Term	Definition / description
IPD	Important protocol deviation
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Drug Regulatory Activities
PD	Protocol deviation
PK	Pharmacokinetic
PT	Preferred term
REP	Residual effect period
RPM	Report planning meeting
SBP	Systolic blood pressure
SAE	Serious Adverse Event
SD	Standard deviation
SDL	Subject data listing
SMQ	Standardised MedDRA query
SOC	System Organ Class
TOC	Table of contents
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
ULOQ	Upper limit of quantification

3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the Clinical Trial Protocol (CTP), and to include detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

This trial statistical analysis plan (TSAP) assumes familiarity with the CTP. In particular, the SAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, and randomisation.

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by [redacted] and several SAS™-based tools (e.g., macros for the analyses of AE data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the Clinical Trial Report (CTR) appendices). Pharmacokinetic (PK) parameters will be calculated using WinNonlin™ software (version 8.1, [redacted]).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

There are no changes in this TSAP compared to the statistical methods described in the CTP.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

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

The calculation of HVPG will be based on the measurements of wedged hepatic venous pressure (WHVP) and free hepatic venous pressure (FHVP).

The average WHVP and the average FHVP will be calculated from the triplicate measurements. Either the average FHVP or the measurement proximal free hepatic venous pressure (PFHVP) will be used as the subtrahend for the calculation of HVPG, which will be rounded to one decimal place.

Based on the judgement of the central reader, if the recorded PFHVP is considered to be more reliable than the average of the recorded triplicate FHVPs, then:

HVPG (mmHg)=average WHVP (mmHg) – PFHVP (mmHg);

if the average of the recorded triplicate FHVPs is considered to be more reliable than the recorded PFHVP, then

HVPG (mmHg)=average WHVP (mmHg) – average FHVP (mmHg).

The quality of the HVPG will be categorized into optimal, sub-optimal and not evaluable based on the judgement of the central reader. A frequency table will be provided to summarize the quality of HVPG tracings measured at baseline and week 8.

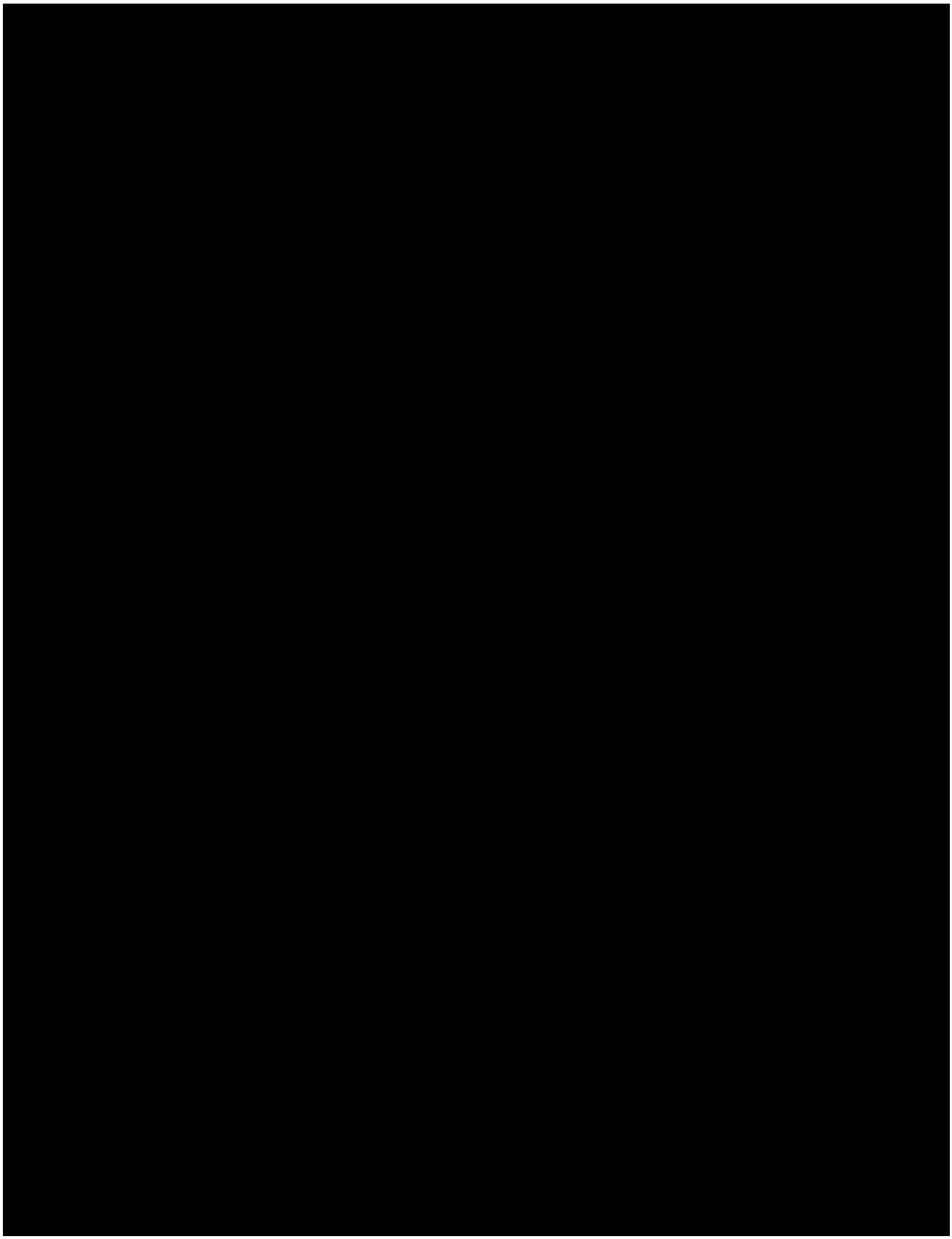
5.1.1 Key secondary endpoint(s)

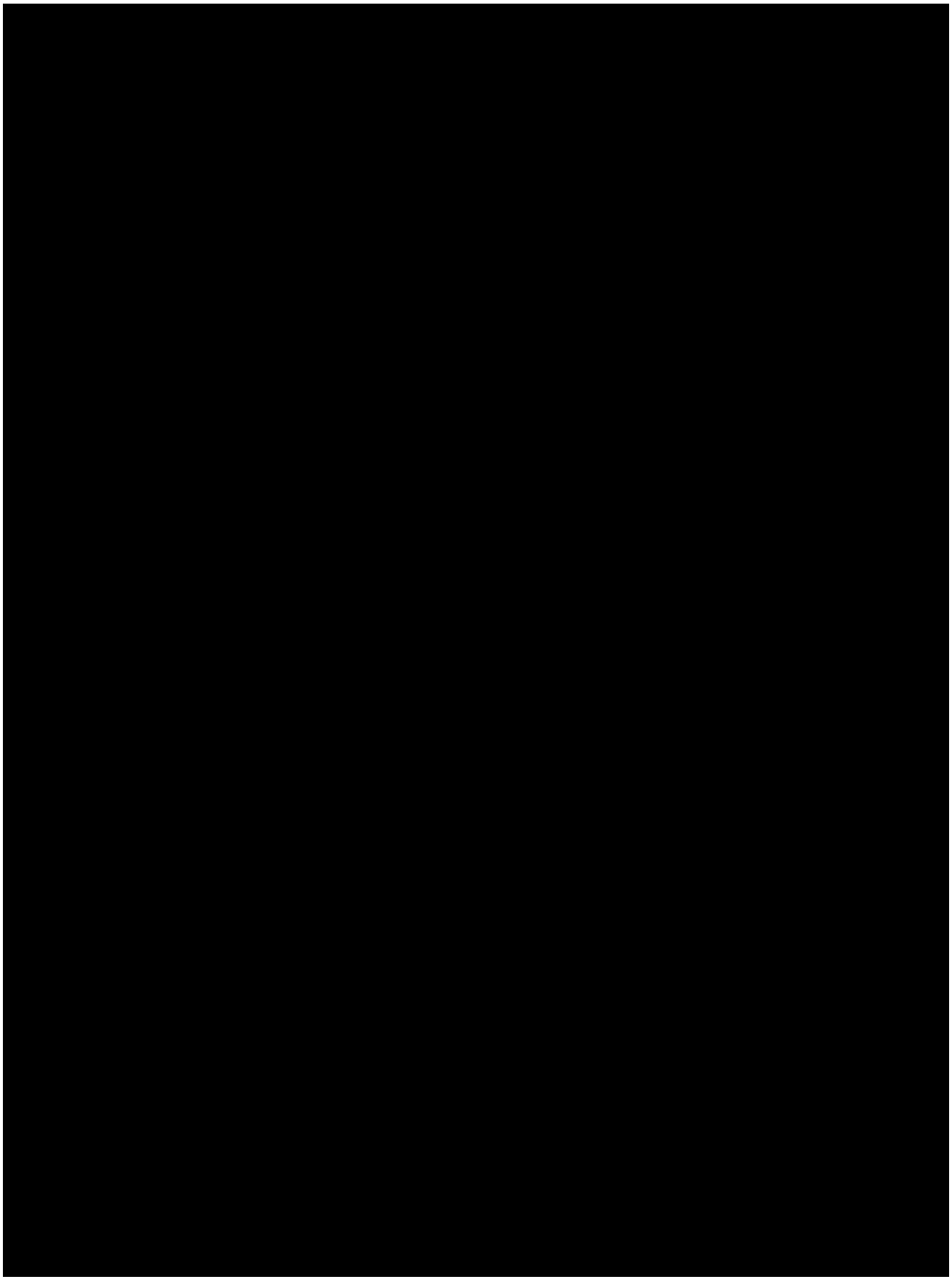
Since there are no key secondary endpoints specified in the CTP, this section is not applicable.

5.2 SECONDARY ENDPOINT(S)

Following secondary endpoints will be analysed:

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





6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on the treatment to be administered, assignment to treatment, and selection of dose, refer to CTP Section 4.

There will be three study phases in this trial: screening, study treatment phase (with avenciguat and avenciguat + empagliflozin) and follow-up.

Table 6.1: 1 Flow chart of analysis phases

Label	Interval	Start date	End date
Screening	Screening	Date of informed consent	Date of first administration of study medication -1
avenciguat [redacted] avenciguat [redacted] + empagliflozin 10mg	On-treatment	Date of first administration of study medication	Date of last intake of study medication + X*
Follow-up*	Follow up	Date of last intake of study medication + X* + 1	Latest of (day of EOS visit, last contact date on EOS page)

*X=1, 3 or REP (7) days for safety laboratory, and AE respectively. X for other variables are defined in Table 6.7: 1. Follow-up phase might not exist, e.g., if the patient's trial termination date is within 7 days after last administration of study drug.

The purpose of the definitions above is to describe all the different study/treatment intervals, to which a patient can be assigned during the course of the trial.

For efficacy analyses of HVPG, data up REP+1 (8 days) after last treatment intake will be considered as on-treatment, because an HVPG measurement at EOT is permitted within 7 days after scheduled EOT (i.e., REP+1 day after last dose) as stated in Section 5.1.1 of the CTP.

The efficacy analyses will follow the intention-to-treat (ITT) principle in assigning patients to treatment groups, i.e., patients will be analysed in the treatment group they were assigned or randomised to.

AEs with an onset during the time of the incorrect study treatment will be listed separately.

6.2 IMPORTANT PROTOCOL DEVIATION

Each protocol deviation must be assessed to determine whether it is an important Protocol Deviation (iPD). The documentation of the iPD categories and handling of iPDs in analysis is included in the DV domain specification and stored within the TMF in EDMS.

The decision about which protocol deviation (PD) could generate exclusion from analysis sets will be taken during the conduction of the trial and finalised at the last report planning meeting (RPM).

Non-important COVID-19 related PDs will only be listed.

6.3 INTERCURRENT EVENTS

The expected intercurrent events (ICEs) 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, pioglitazone, GLP1-agonists and vitamin E concomitant therapy
- Occurrence of a decompensation event
- Premature discontinuation of assigned trial medication

The strategies for handling those intercurrent events in this trial are as follows:

Treatment Policy: This is the effect of randomizing patients to a treatment arm regardless of treatment actually being taken. All intercurrent events will be handled according to the treatment policy approach as defined in ICH E9(R1). This will be used as the **primary strategy** of implementing the Estimand Concept (EC).

6.4 SUBJECT SETS ANALYSED

The subject sets will be used as defined in the CTP, Section 7.2.1. These include the Treated set (TS) and Full analysis set (FAS). [redacted]

- Screened set (SCR) – this analysis set includes all patients having signed informed consent. The SCR will be used for analyses of patient disposition.

[redacted]

The discussion on all exceptional cases and problems and the decisions on the allocation of patients to populations will be made at latest at DBLM.

In Table 6.4:1 the subject sets which are to be used for each class of endpoint are illustrated.

Table 6.4: 1 Subject sets analysed

	Subject set			
Class of endpoint	SCR	TS	FAS	[redacted]
Disposition	X			
Primary endpoint			X	
Secondary efficacy endpoints			X	
Safety endpoints & treatment exposure		X		
Demographic/baseline endpoints		X		
[redacted]				

Handling of Treatment Misallocations in Analysis Sets

If a subject entered the trial but was not treated, they will be reported under their randomised/assigned treatment group for efficacy analysis according to FAS. Such subjects are excluded from the safety analyses since no study medication was taken.

If a subject is randomised but took incorrect treatment during the study,

- For efficacy analyses according to the FAS, subjects who took incorrect treatment will be reported under their randomised treatment group.
- For safety analyses based on TS, the actual treatment will be used as below:
    - If a patient took at least one dose of empagliflozin, then the patient will be reported under the treatment group of avenciguat + empagliflozin.

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

6.6.1 Efficacy data

No imputation of missing data is planned for the efficacy endpoints.

6.6.2 Safety data

Missing safety data will not be imputed.

6.6.3 Missing dates and times

Missing or incomplete AE dates are imputed according to company standards (2).

If the date of first drug administration is missing but the patient was entered, the date of the first drug administration will be set to the date of entering the trial. If the date of first administration is partially missing with the month and year present, the day will be set to the date of entering the trial if entering the trial was in the same month. If entering the trial was in the month prior to the first drug administration the missing day will be imputed as the first day of the month.

Partial start and stop dates for concomitant therapies will be imputed to enable subsequent calculation (but not for display) by the following "worst case" approach:

- If the day of the end date is missing, then the end date is set to last day of the month (or to the patient's trial completion date, whichever is earlier).
- If the day and month of the end date are missing, then the end date is set to 31st of December of the year (or to the patient's trial completion date if it is earlier than 31st December of the year).
- If the day of the start date is missing, then the start date is set to first day of the month.
- If the day and month of the start date are missing, then the start date is set to 1st January of the year.

All other cases need to be assessed by the trial team on an individual basis, using above points as guidance.

6.6.4 Time since first diagnosis

For incomplete information on the date of the first diagnosis (both of cirrhosis and of chronic liver disease), time since first diagnosis will be calculated as follows:

- If the year of first diagnosis is unknown, then the time since diagnosis will be set to missing.
- If day and month of the first diagnosis are unknown, time since first diagnosis will be calculated as if diagnosed on the 30th June of that year.
- If only the day of the first diagnosis is unknown, time since diagnosis will be calculated as if diagnosed on the 15th of that month.

[redacted]

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Regarding efficacy and safety endpoints, the term “baseline” refers to the last observed measurement prior to administration of any study medication.

Measurements taken prior to the first intake of study medication will be considered pre-treatment values. Pre-treatment values will be assigned to a visit according to the nominal visit number as recorded on the eCRF or as provided by the laboratory.

In general, the date of the first drug administration will be used to separate pre-treatment from on-treatment values. Measurements taken after first trial medication intake will be considered on-treatment values if they have been obtained up to end of the parameter specific follow-up period as defined in Table 6.7:1 below and will be assigned to the corresponding study medication for efficacy and safety analyses.

Measurements taken after the end of the endpoint specific follow-up period will be considered post-treatment values.

Table 6.7: 1 Parameter specific follow-up period for the assignment to treatment phase

Endpoint	Last day of assignment to treatment phase (days after study medication stop date)
Efficacy	
HVPG	8 (REP + 1)
[redacted]	
Safety	
Adverse events	7
Safety laboratory measurements	3
Vital signs (including body weight, blood pressure)	1

For derivation of the last value on treatment, minimum value on treatment, and maximum value on treatment, all values from the relevant phase (whether or not collected in any time window; see Table 6.1:1 for definition of the trial phases) will be considered; these will be derived for analysis of laboratory and vital signs data. For identification of potentially clinically significant abnormal laboratory values, all values (whether selected in any time window) up to 7 days after last treatment intake will be considered.

On-treatment efficacy, safety [redacted] measurements will be assigned to visits based on the extended time windows around the planned visit dates, defined relative to the day of first trial medication intake (see Table 6.7:2).

Table 6.7: 2 Time windows for assignment of measurements to visits for statistical analysis

Visit number /name	Visit label	Planned day [B]	Time window (Days)				
			Window (per CTP)	Start (per CTP)	End (per CTP)	Start (extended)*	End[A] (extended)[#]
V1	Screening	-42				-∞	0
			On-treatment				
V2	Week 0	Day 1	N/A	1	1	≤1	1
V3	Week 1	Day 8	+2	8	10	2	11
V4	Week 2	Day 15	+2	15	17	12	22
V5	Week 4	Day 29	+2	29	31	23	36
V6	Week 6	Day 43	±3	40	46	37	50
V7	Week 8/ EoT	Day 57	±3	54	60	51	Study medication stop date + X[C] days
			Off-treatment				
V8	Week 12/ EoS	Day 85	±5	80	90	Study medication stop date + X days+1	Day of last follow-up

[A] In case of premature discontinuation of the study medication, an early EoT visit has to be performed within 7 days of medication stop date. If such an EoT Visit falls into the time window of a previous visit, measurements will be assigned to this previous visit and the visit value will be determined as described above. In this case, the time window for the visit that includes the early EoT visit will end X days after the study medication stop date, including Day X. Patients will then be asked to continue in the study according to the visit schedule. Off-treatment measurements will be assigned to visits in the same manner.

[B] Days are counted relative to the day of first treatment, which is defined as Day 1.

[*] Start (extended): End of extended window of last visit+1

[#] End (extended): Midpoint of planned days between current visit and next visit

[C] X is the parameter specific follow-up period for the assignment to treatment phase, refer to Table 6.7:1 for the details.

The midpoint between two on-treatment visits defines the end of a time window, with the midpoint being included in the time window of the preceding visit. The end of the time window of the last on-treatment visit (end of treatment (EoT)) is endpoint dependent (Table 6.7:1).

Repeated and unscheduled efficacy and safety measurements will be assigned to the nominal visits and listed in the subject data listing according to the time windows described above. Only one observation per time window will be selected for analysis at an on-treatment visit - the value which is closest to the protocol planned visit day will be selected. If there are two

observations which have the same difference in days to the planned day, the first value will be selected. If there are two observations on the same day, the first value will be selected. If there are multiple values within the time window of the last visit, including a value on the last day of drug intake, the value on the last day of drug intake is used as the value of the last visit.

Data prior to Day 1 of trial medication will be based on nominal visits and time windowing will not be applied. For these time points, data from the scheduled visit will always be selected if they are collected correctly. Unscheduled visits will only be considered if no correct data from the scheduled visit is available. If no correct data from a scheduled visit is available and multiple unscheduled correct values are available for a visit, the first correct value will be selected.

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI guideline "Standards for Reporting of Clinical Trials and Project Summaries" (3).

Disposition of the patient population participating in the trial will be summarized by the presentation of the frequency of patients screened, screened but not entered, entered but not treated, entered and treated, who completed planned treatment period, who were prematurely discontinued from trial medication by reasons, who completed the study, and who prematurely discontinued from the study.

A frequency of patients with iPDs will be presented by treatment group for treated set. The frequency of patients in different analysis sets will also be presented for each treatment group. The iPDs per patient will be listed indicating whether the iPD led to exclusion from patient sets analysed.

For tables presenting descriptive analysis of the endpoints and other variables, the set of summary statistics is: N (number of patients with nonmissing values) / Mean / SD / Min / Q1 (lower quartile) / Median / Q3 (upper quartile) / Max.

Statistical parameters will be displayed to a defined number of decimal places as specified in the BI guideline "Reporting of Clinical Trials and Project Summaries" (3).

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as percentage (%) relative to the respective treatment group. Percentages will be based on all patients in the respective patient set whether they have non-missing values or not. Percentages will be rounded to one decimal place. The category missing will be displayed if and only if there are actual missing values.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section.

Descriptive statistics for demographic parameters and baseline characteristics will be presented by treatment, based on the TS.

For the continuous variables described below, categories are defined in Table 7.1:1. These variables will be presented according to the number and percentage of patients in each category, in addition to the display of the summary statistics for continuous variables.

Table 7.1: 1 Categories for summary of continuous variables

Variable	Categories
Age (years)	< 50 50 to < 65 65 to < =75 >75 < 65 ≥ 65
Weight (kg)	≤ 70 > 70 to ≤ 80 > 80 to ≤ 90 > 90
BMI (kg/m^2)	< 25 25 to < 30 ≥ 30
eGFR ($mL/min/1.73\ m^2$)	≤ 30 > 30 to ≤ 45 > 45 to ≤ 60 > 45 to ≤ 60 > 60 to ≤ 90 > 90
Time since first diagnosis of (years)	≤ 1 > 1 to ≤ 5 > 5 to ≤ 10 > 10
Baseline HVPG (mmHg)	≤ 12 >12 ≤ 15 >15

7.2 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report.

The compliance based on TS will be described as collected in the eCRF. Number and percentage of patients with compliance in following categories will be displayed at each visit since week 1:

- "Yes",
- "No" and,
- "Missing".

7.3 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report. Analyses of the concomitant diseases and medication as well as non-drug therapies will be based on TS.

Concomitant diseases will be coded according to the most recent version of Medical Dictionary for Drug Regulatory Activities (MedDRA).

Concomitant medication will be coded according to the most recent version of the World Health Organisation – Drug Dictionary (WHO-DD).

A medication/non-drug therapy will be considered concomitant to treatment if it:

- is ongoing at the start of trial medication intake
- starts within the on-treatment period (see Section 6.1 for a definition of study analysis phases).

Concomitant medication use will be summarised with frequency and percentage of patients by Anatomical Therapeutic Chemical 3 (ATC3) class and preferred name.

7.4 PRIMARY OBJECTIVE ANALYSIS

The primary endpoint for this study is the percentage change from baseline in HVPG from baseline after 8 weeks of treatment.

7.4.1 Main analysis

For the primary endpoint, the analysis of covariance (ANCOVA) will be used. The analysis will be performed on the FAS and include on-treatment HVPG only. If a patient misses the Week 8 visit, the missing data will not be imputed.

The statistical model will be:

Percentage HVPG change from baseline at Week 8 = overall mean + HVPG baseline + treatment + random error

This model includes treatment as fixed classification effects and baseline HVPG as a linear covariate. The random error is assumed to be normally distributed with mean 0 and variance σ^2. The analysis will only be used for estimation of treatment effects without performing statistical tests.

The main analysis will implement the primary estimand defined in Section 6.3 and be performed on FAS. All data collected after the intercurrent events will be used for the analysis. The number of patients reporting each type of intercurrent event will be summarized for overall and each treatment group.

If after all the steps above have been investigated without successful model convergence, then an ANCOVA (Analysis of Covariance) model at Week 8 only, will be performed. If the above sequence of methods does not lead to convergence for a particular subgroup, then that analysis will not be performed or reported.

[redacted]

7.4.4 Supplementary analysis

For primary endpoint, the analysis in Section 7.4.1 will be repeated in

- FAS excluding patients with down-titration or dose-interruption

7.5 SECONDARY OBJECTIVE ANALYSIS

7.5.1 Key secondary objective analysis

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 Subgroup analysis

No subgroup analyses are planned for the analysis.

7.5.3 Secondary objective analysis

The secondary endpoints for this study are described in CTP Section 2.1.3.

For the occurrence of CTCAE grade 3 (or higher) hypotension or syncope based on Investigator judgement and the occurrence of discontinuation due to hypotension or syncope,

the numbers and percentages of patients with those events will be presented jointly and also separately.

For the occurrence of decompensation events, categories are defined in Table 7.5.3:1.

Table 7.5.3:1 Categories for decompensation events

Categories	Scope	Definition
Acites		PT - 'Ascites' PT - 'Bacterascites' PT - 'Haemorrhagic ascites'
Variceal haemorrhage	Narrow Narrow Narrow Broad Broad Broad	PT - 'Oesophageal varices haemorrhage' PT - 'Oesophageal haemorrhage' PT - 'Bleeding varicose vein' HLT – 'Gastric and oesophageal haemorrhages' HLT – 'Non-site specific gastrointestinal haemorrhages'
Hepatic encephalopathy	Narrow Narrow Broad Broad	PT - 'Hepatic encephalopathy' PT - 'Coma hepatic' PT - 'Hyperammonaemic encephalopathy' PT - 'Hyperammonaemic crisis'
Other		PT - 'Cardiohepatic syndrome' PT - 'Hepatorenal syndrome' PT - 'Hepatorenal failure' PT - 'Hepatic hydrothorax' PT - 'Hepatopulmonary syndrome'

For all the secondary endpoints, only descriptive statistics will be presented.

[redacted]

7.7 EXTENT OF EXPOSURE

A descriptive statistics table with mean, SD, median and range of the number of days a patient was on treatment will be provided for the treated set. The tables will also provide the sum total of the time that all patients pooled together were on treatment. A separate listing will be created for patients who switched treatment, had dose interruption or dose down-titration any time indicating exposure to each treatment.

A frequency table of number and percent of patients belonging to each categorical range of exposure weeks will be provided as well. The following are the categories of exposure-ranges (in weeks): “0 to 4 weeks”; “> 4 to 8 weeks” and “>8 weeks”.

No temporary treatment interruption period will be reported.

7.8 SAFETY ANALYSIS

All safety analyses will be performed based on the TS following BI standards. Additionally, AE reported to be related to study procedures will be listed based on the SCR.

7.8.1 Laboratory data

The analyses of laboratory parameters will be descriptive in nature and will be based on BI standards (7). Note that data from the central Laboratory will be used for all displays described below, unless otherwise specified.

For continuous safety laboratory parameters standardized and normalized values will be derived as well as the differences to baseline. Normalisation means transformation to a standard unit and to a standard reference range. The process of normalisation, handling of repeat values at the same visit for by-visit displays, as well as standard analyses for safety laboratory data are described in the BI guidance for “Handling, Display and Analysis of Laboratory Data” (7). All analyses considering multiple times of the ULN (as described below) will be based on standardised and not normalised values.

Laboratory parameters will be shown in conventional units. Where conventional units differ from SI units, analyses will be repeated on SI units in the appendix.

Laboratory values will be compared to their reference ranges and frequency tables will be provided for the number of patients within and outside the reference range at baseline and the last measurement on treatment. Descriptive statistics will be provided by treatment group and total for baseline, last value on-treatment and for changes from baseline to last value on treatment. Frequency tables will summarise the number of patients with potentially clinically significant abnormalities.

Both on-treatment and post-treatment values of the following lab parameters will be presented graphically. The values after the treatment period will be assigned to the follow-up (EoS) period.

- Haematocrit
- Haemoglobin
- RBC count / erythrocytes
- WBC / leukocytes
- Platelet count / thrombocytes
- Reticulocytes
- INR
- ALT
- Alkaline phosphatase
- AST
- Bilirubin (total)
- Albumin
- gamma-GT
- eGFR

Only patients with at least one available on-treatment value will be included in the analysis of an individual laboratory parameter. All individual data will be presented in listings.

To support analyses of liver related adverse drug effects, the frequency of patients with AST and/or ALT ≥ 3xULN combined with the total bilirubin ≥ 2xULN in a 30-day period after AST/ALT elevation will be displayed, stratified by alkaline phosphatase < 2xULN and ≥ 2xULN (a patient can potentially be in both alkaline phosphatase strata in case of multiple AST/ALT and bilirubin elevations). The start of the 30-day time span is triggered by each liver enzyme elevation above defined thresholds. This analysis will be based on standardised laboratory values.

A graphical analysis of the ALT and total bilirubin during the on-treatment period will also be performed; the so called eDISH plot. In the graph, for each subject, the peak total bilirubin is presented as a fold increase over the ULN against the peak ALT as a fold increase over the ULN, on a log 10 scale. The measurements displayed for total bilirubin and ALT may, or may not, occur on the same date. Two reference lines, 2xULN for total bilirubin and 3xULN for ALT, are drawn onto the graph to divide the plane into four quadrants. Normal cases are in the lower left quadrant, potential DILI cases are in the upper right quadrant (Hy's Law quadrant), while the lower right quadrant is known as the Temple's corollary range (ALT ≥ 3xULN and total bilirubin < 2xULN). The same graphical analysis will be performed for AST and total bilirubin during the on-treatment period as well. Details on patients with elevated live enzymes will be listed.

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as AEs (during the trial). If judged clinically relevant by the investigator and will be analysed as such.

7.8.2 Adverse Events

AEs will be coded with the most recent version of MedDRA coding dictionary. Patients will be analysed according to the actual treatment received.

Any clinically significant new finding in the physical examination, vital signs (blood pressure and pulse symptoms) and in the 12-lead ECG starting after visit 2 will be considered as an AE and will be reported as such.

The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and not on the number of AEs.

7.8.2.1 Assignment of AEs to treatment

In general, the analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs occurring between first drug intake till 7 days (residual effect period – REP) after last drug intake will be assigned to the on-treatment period. All AEs occurring before first drug intake will be assigned to ‘screening’ and all AEs occurring after last drug intake + REP of 7 days will be assigned to ‘follow-up’ (for listings only). For details on the treatment definition, see Section 6.1.

If only the start date of an AE is collected (without the start time), any AE occurrence on the same day as the first avenciguat administration will be assigned to the on-treatment phase.

In general, tables will only present AEs assigned to the first treatment taken except drug-related AEs which will be presented as actual treatment taken at each given timepoint. AEs and serious adverse events (SAEs) assigned to the following phases: screening, on-treatment, post-treatment will be listed.

7.8.2.2 Analysis of other significant AEs

Other significant AEs will be reported and summarised according to ICH E3 criterion (5). Thus, AEs classified as 'other significant' will include those non-serious adverse events with ‘action taken = discontinuation’ or ‘action taken = dose reduced’.

7.8.2.3 AE summaries

An overall summary of adverse events will be presented.

The frequency of patients with adverse events will be summarised by treatment, primary SOC and PT. The SOC will be sorted by frequency, PTs will be sorted by frequency (within SOC). AEs which were defined as secondary endpoints will be summarised separately. AEs will also be reported by intensity according to the maximum Common Terminology Criteria for Adverse Events (CTCAE). Separate tables will be provided for patients with other significant AEs according to ICH E3 (5), adverse events of special interest (AESI), for patients with serious adverse events, for patients with AEs leading to discontinuation, for patients with AEs leading to dose reduction, for patients with drug-related AEs and for patients with fatal AEs. Note that for drug-related AEs, separate tables will be prepared for treatment group 4 – one for AEs related to avenciguat and one for AEs related to empagliflozin. A listing of AEs related to study procedure will be prepared based on enrolled set.

For further details on summarisation of AE data, please refer to "Handling of missing and incomplete AE dates" (2) and "Analysis and Presentation of Adverse Event data from Clinical Trials" (6).

7.8.2.4 AEs of special interest (AESIs)

The protocol defines the following adverse event as AESI:

- 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 CTP Section 3.3.4.1 and CTP Appendix 10.2.
- Ketoacidosis
  If metabolic acidosis, ketoacidosis, or diabetic ketoacidosis (DKA) is suspected further investigations should be done according to medical judgement and the clinical course until a diagnosis is made and/or the patient is recovered.

More details refer to CTP Section 5.2.6.1.4.

An independent Adjudication Committee will adjudicate certain hepatic events for the severity and causal relationship with the trial medication. Adjudication assessments will be incorporated to the database. Frequency tables will be provided for the PTs in the specified SMQs of events and for the adjudication endpoints. Tables will be provided for events qualifying for adjudication and then separately the events that were confirmed or non-assessable.

7.8.2.5 User-defined adverse event category (UDAEC)

UDAEC will be summarized by dose group, primary system organ class and preferred term. In summary, Table 7.8.2.5:1 provides the definition of UDAECs according to AE category or Standardized MedDRA Query (SMQ).

Table 7.8.2.5: 1 Definition of continuous UDAEC

Category	Safety topic	Definition
UDAEC	Hypotension	Investigator-reported, as a dedicated AE category on the AE eCRF page
UDAEC	Syncope	Investigator-reported, as a dedicated AE category on the AE eCRF page
UDAEC	Acute kidney injury	SMQ 'Acute renal failure', narrow scope
UDAEC	Peripheral edema	SMQ 'Haemodynamic oedema, effusions and fluid overload'
UDAEC	Bleeding	SMQ 'Haemorrhages', narrow scope
UDAE	Liver events	Narrow sub-SMQ 'Liver related investigations, signs, and symptoms', narrow sub-SMQ 'Cholestasis and jaundice of hepatic origin', narrow sub-SMQ 'Hepatitis, non-infectious'

Category	Safety topic	Definition
		and narrow sub-SMQ 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions'

Summary of hypotension and syncope will be presented for both patient-based and event-based analyses. ae

Analysis on hypotension based on baseline BP and the lowest BP during the episode will be carried out. Criteria for significant (vs. non-significant) hypotensive episode are:

- Baseline SBP <=140: decrease $\left(\frac{\text{lowest SBP during the episode} - \text{baseline SBP}}{\text{baseline SBP}}\right) \geq 30\%$;
- Baseline SBP >140: decrease $\left(\frac{\text{lowest SBP during the episode} - \text{baseline SBP}}{\text{baseline SBP}}\right) \geq 40\%$;
- Or lowest SBP during the episode <90.
- Baseline DBP <=70: $\left(\frac{\text{lowest DBP during the episode} - \text{baseline DBP}}{\text{baseline DBP}}\right) \geq 30\%$;
- Baseline DBP > 70: $\left(\frac{\text{lowest DBP during the episode} - \text{baseline DBP}}{\text{baseline SBP}}\right) \geq 40\%$;
- Or lowest DBP during the episode <50.
- Lowest mean arterial pressure (MAP=DBP+1/3(SBP-DBP)) during the episode<70.

7.8.3 Vital signs

The analyses of vital signs (blood pressure and pulse rate) will be descriptive in nature. Descriptive statistics of vital signs over time during treatment period and post-treatment period (pre-dose, 1 hour and 2 hour) and for the difference from baseline and pre-dose will be provided by treatment, including the last value, the minimum value, and the maximum value within the study period as described in Table 6.1:1. Figures for change from baseline and change from pre-dose for on-treatment visit and post-treatment visit will be provided as well.

7.8.4 ECG

Abnormal findings in 12-lead ECG will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator and will be analysed as such.

No separate listing or analysis of ECG data will be prepared.

7.9 OTHER ANALYSIS

7.9.1 Ultrasound

Descriptive analysis of change from baseline of portal vein diameter at week 8 will be provided. A listing of all the collected data from the ultrasound CRF page for each patient will be provided.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

Not applicable as no blinding procedure is needed.

9. REFERENCES

1.	*CPMP/ICH/363/96*: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9; Note for Guidance on Statistical Principles for Clinical Trials, current version
2.	*BI-KMED-BDS-HTG-0035:* “Handling of missing and incomplete AE dates”, current version; KMED.
3.	*KM Asset BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version, KMED.
4.	*BI-KMED-TMCP-MAN-0012*: “Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics”, current version; KMED.
5.	*CPMP/ICH/137/95:* “Structure and content of clinical study reports”, ICH Guideline Topic E3; Note for Guidance on Structure and Content of Clinical Study Reports, current version.
6.	*KM Asset BI-KMED-BDS-HTG-0066:* “Analysis and Presentation of Adverse Event data from Clinical Trials”, current version, KMED.
7.	*KM Asset BI-KMED-BDS-HTG-0042:* " Handling, Display and Analysis of Laboratory Data", current version; KMED

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	20-JUN-24	[redacted]	None	This is the final TSAP.