Boehringer Ingelheim

TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c43185880-01**
BI Trial No.:	1366-0055
Title:	Randomised, double-blind, placebo-controlled and parallel group trial to investigate the effects of one dose (up-titration to a fixed dose regimen) of oral BI 685509 on portal hypertension after 8 weeks treatment in patients with clinically significant portal hypertension (CSPH) in decompensated cirrhosis after their first decompensation event, who are stabilized CTP 5-7
Investigational Product(s):	BI 685509 (Avenciguat)
Responsible trial statistician(s):	[redacted] Phone: [redacted]
Date of statistical analysis plan:	01 JUL 2024
Version:	1.0
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2. LIST OF ABBREVIATIONS

Term	Definition / description
ALQ	Above Limit of Quantification
ALT	Alanine transaminase
ANCOVA	Analysis of Covariance
AST	Aspartate transaminase
BLQ	Below Limit of Quantification
BMI	Body mass index
DBP	Diastolic blood pressure
FHVP	Free hepatic venous pressure
Fib-4	Fibrosis-4
HVPG	Hepatic Venous Pressure Gradient
LLOQ	Lower limit of quantification
PFHVP	Proximal free hepatic venous pressure
RS	Randomised Set
SBP	Systolic blood pressure
SD	Standard deviation
TS	Treated Set
ULN	Upper Limit of Normal
ULOQ	Upper limit of quantification
WHVP	Wedged Hepatic Venous Pressure

3. INTRODUCTION

As per ICH E9 (9.1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP 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, randomization.

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by [redacted], and a number of 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

The Avenciguat program in patients with clinically significant portal hypertension (CSPH) is decided to be discontinued in May 2024. No subject has finished the 8-week treatment duration, leading to no HVPG data at Week 8 collected. Therefore, planned analysis around HVPG data in the CTP, i.e.,

- percentage change in HVPG from baseline after 8 weeks of treatment,
- occurrence of a response, which is defined as > 10% reduction from baseline HVPG after 8 weeks of treatment,

will not be performed. Only listing will be prepared.

Consequently, the reporting of intercurrent event, which supports HVPG analysis, is no longer of interest. All subjects are decided to be early discontinued.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

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

The average wedged hepatic venous pressure (WHVP) and the average free hepatic venous pressure FHVP (FHVP) will be calculated based on the triplicate measurements.

Either the average FVPG or the measured proximal free hepatic venous pressure (PFHVP) will be used as the subtrahend for the calculation of HVPG (rounded to one decimal place).

Based on the judgment of the central reader, if the recorded PFHVP is considered to be more reliable than the recorded FHVP, then:

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

if the recorded FHVP is considered to be more reliable than the recorded PFHVP, then

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

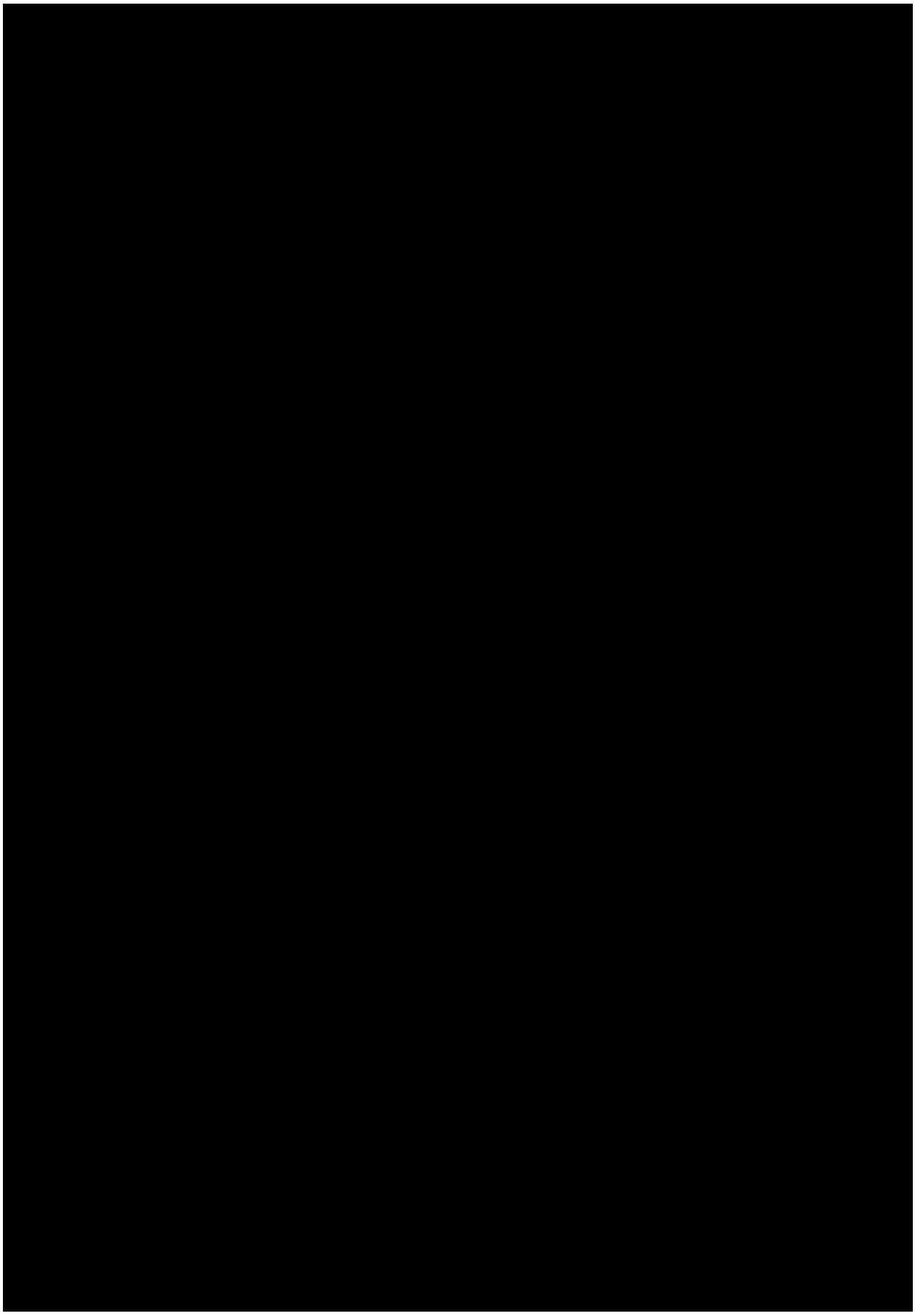
5.2 SECONDARY ENDPOINT(S)

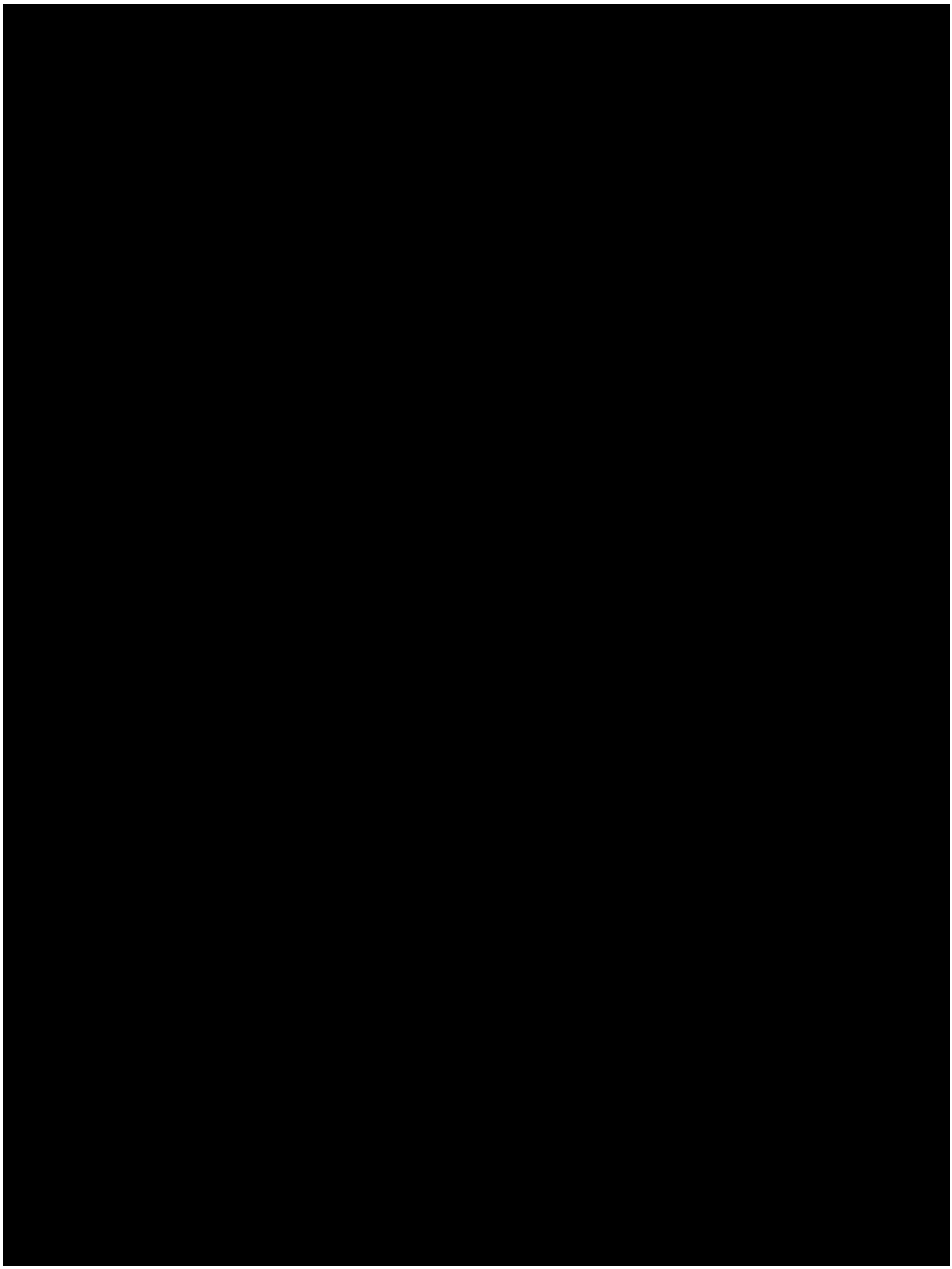
5.2.1 Key secondary endpoint(s)

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

5.2.2 Secondary endpoint(s)

The secondary endpoints will be used as defined in CTP Section 2.1.3.





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 treatment study phases in this trial: screening, double-blind study treatment phase (with Avenciguat and matching placebo) and follow-up.

Table 6.1: 1 Flow chart of analysis phase

Label	Interval	Start date	End date
Screening	Screening	Date of informed consent	Date of first administration of double-blind study medication - 1
Placebo/ Avenciguat 3mg	On-treatment	Date of first administration of double-blind 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 (date of EOS visit, last contact date on EOS page)

* X=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. Note that the term "treatment regimen" can also cover time periods with no active treatment.

For efficacy analyses of HVPG, data up to REP+1 (8 days) after last treatment intake will be considered as on-treatment, because a HVPG measurement at EOT is allowed to be done within 7 days after scheduled EOT (i.e, REP+1 days after last dose) as Section 5.1.1 of the CTP states "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)

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

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

6.2 IMPORTANT PROTOCOL DEVIATIONS

Each protocol deviation must be assessed to determine whether it is an important Protocol Deviation (iPD). The documentation of the iPD categories and how to handle iPDs in the analysis are done in the DV domain.

Handling of iPDs in analysis is included in the DV domain specifications 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 course of the study and finalised at the last report planning meeting (RPM), i.e. before unblinding.

6.3 INTERCURRENT EVENTS

Not applicable as described in Section 4.

6.4 SUBJECT SETS ANALYSED

The subject sets will be used as defined in the CTP, Section 7.2.1. These include the Enrolled set (ES), Randomised set (RS), Treated set (TS) and Full analysis set (FAS). In addition, the following subject sets for the analysis of PK parameters and biomarkers will be used.

- Screened set (SCR) – this analysis set includes all patients having signed informed consent. The SCR will be used for analyses of patient disposition
- PK parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection ‘Pharmacokinetics’). Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value to the statistical assessment. Descriptive analyses of PK parameters will be based on the PKS.
- Biomarker set (BMS): This set includes all subjects from the Treated Set (TS) who provide at least one evaluable measurement assessing the liver or spleen stiffness using FibroScan® or an exploratory biomarker (refer to CTP Section 5.4), that was not excluded due to a protocol deviation relevant to the evaluation of biomarkers.

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

	Subject set					
Class of endpoint	SCR	RS	TS	FAS	PKS	BMS
Disposition	X					
Primary endpoint				X*		
Secondary efficacy and further efficacy endpoints				X*		
Secondary and further safety endpoints (including liver decompensation) & treatment exposure			X			
Demographic/baseline endpoints		X				
Further PK endpoints					X	
Further biomarker endpoints						X

* Planned analysis around HVPG data in the CTP will not be performed, as described in Section 4.

Handling of Treatment Misallocations in Analysis Sets

If a patient was administered incorrect treatment during the study, for efficacy analyses:

- subjects who took incorrect treatment will be reported under their randomized treatment group. In the case of stratification error at randomisation, the subjects will be analyzed according to the stratum to which they actually belong to (regardless of any mis-assignment to treatment based on identification of the wrong stratum from IRT), as such an error occurs before randomisation and is therefore consistent with regulatory guidance.

If a patient was administered incorrect treatment during the study, then for safety the following will be used in addition:

- If a patient is planned to receive Avenciguat, then patients will be reported under the planned treatment from the randomisation visit for safety analyses because the overall safety profile is expected to be driven by the amount of drug received in totality over the entire treatment duration. It is not expected that the safety profile will deviate from the planned treatment regimen if the subject receives only one or two kits of the incorrect medication at only some dosing occasions.
- If a patient is planned to receive Placebo, then patients will be reported under their randomised treatment group for safety analysis if the patient was administered no Avenciguat kits at any visit. If the patient was administered at least one kit of BI

685509 during the treatment period, then the patient will be assigned to Avenciguat treatment group.

[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.

An analysis of the changes from baseline to the last available value under treatment and the minimum and maximum post baseline will be determined for quantitative safety laboratory variables.

6.6.3 Missing dates and times

Missing or incomplete AE dates are imputed according to BI standards (9.2).

If the date of first drug administration is missing but the patient was randomised, the date of the first drug administration will be set to the date of randomisation. If the date of first administration is partially missing with the month and year present, the day will be set to the date of randomisation if randomisation was in the same month. If randomisation 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 of cirrhosis, 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 calculated as if diagnosed on the 15th of that month.

6.6.5 PK data

Missing data of PK data are handled according to BI standards (9.4).

6.6.6 Biomarker data

For disease specific protein markers (refer to CTP Section 5.4) the following handling of data below or above the limit of quantification will be applied:

- BLQ data will be replaced by 0.5 · LLOQ. Hereby LLOQ will be the maximum used lower reference limit for classification of BLQs. All values lower than LLOQ will be imputed (regardless of whether they are classified as BLQ or not).
- ALQ data will be replaced by ULOQ, if ULOQs are available and are greater than observed study values (i.e. the highest solution was applied for the measurement). Otherwise, ALQ data will be excluded from the analysis.

Otherwise, missing data (NOS - no sample, NOR - no valid result, NOA - not analysed) will not be imputed.

The handling of other biomarkers (e.g. genetic variants in disease genes) will be given in a separate biomarker SAP.

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)
Fibroscan data	8
Biomarkers	1
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 and biomarker 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	Time window (Days)				
			Window (per CTP)	Start (per CTP)	End (per CTP)	Start (extended)*	End (extended)*
V1	Screening	-28				-∞	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	±5	52	62	51	Study medication stop date + X[#]days
			Off-treatment				
V8	Week 10/ EoS	Day 71	±5	66	76	Study medication stop date + X[#] days +1	Day of last follow-up value

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
X= 3 days for safety laboratory; X=1 day for biomarkers and vital sign, respectively; X= 8 days (REP +1) for HVPG and fibroscan data.

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" (9.3).

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 and treated, entered but not treated, who completed Week 8 visit (V7), who were prematurely discontinued treatment by reason, who completed the study, and who prematurely discontinued study.

A frequency of patients with iPDs will be presented by treatment group for TS. 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 analyzed.

For tables presenting descriptive analysis of the endpoints and other variables, the set of summary statistics are:
N (number of patients with non-missing 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" (9.3).

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.

For PK analyte concentrations, as well as PK parameters, the following descriptive statistics will additionally be calculated:

- CV arithmetic coefficient of variation
- gMean geometric mean
- gCV geometric coefficient of variation
- P10 10th percentile
- Q1 1st quartile
- Q3 3rd quartile
- P90 90th percentile

The data format for descriptive statistics of plasma concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by

the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits.

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 RS.

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 > 60 to ≤ 90 > 90
Time since first diagnosis of (years)	≤ 1 > 1 to ≤ 5 > 5 to ≤ 10 > 10
Baseline HVPG	≤ 12 > 12 ≤ 15 > 15

7.2 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 RS.

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 Table 6.1:1 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.

7.3 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 (visit 3):

- “Yes”,
- “No”, and
- “Missing”.

7.4 PRIMARY OBJECTIVE ANALYSIS

7.4.1 Main analysis

As described in Section 4, planned analysis around HVPG data in the CTP, including primary object analysis, will not be performed.

7.4.4 Supplementary analysis

No supplementary analyses are planned.

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 Secondary objective analysis

7.5.2.1 Main analysis

The secondary endpoints for this study are described in CTP Section 2.1.3 and only descriptive statistics will be presented.

For the occurrence of decompensation events, categories are defined in Table 7.5.2:1.

Table 7.5.2:1 Categories for decompensation events

Categories	Scope	Definition
Acites		PT - 'Ascites' PT - 'Bacterascites' PT - 'Haemorrhagic ascites'
Variceal haemorrhage	Narrow Narrow Narrow 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'

[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".

No temporary treatment interruption (≤ 3 doses) 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 Adverse Events

AEs will be coded with the most recent version of MedDRA coding dictionary. Patients will be analyzed 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 (randomisation visit) 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.

7.8.1.1 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 Table 6.1:1.

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, in-text AE 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, each treatment group (placebo, Avenciguat), post-treatment for each treatment group will be listed.

7.8.1.2 Analysis of other significant AEs

Other significant AEs will be reported and summarised according to ICH E3 criterion (9.5). Thus, AEs classified as 'other significant' will include those non-serious adverse events with ‘action taken = discontinuation’ or ‘action taken = dose reduced’.

7.8.1.3 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 and 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 (9.5), for patients with serious adverse events, for patients with AEs leading to dose reduction, for patients with AEs leading to discontinuation, for patients with AEs leading to death, for patients with drug-related AEs, and drug-related serious AEs.

For further details on summarisation of AE data, please refer to “Handling of missing and incomplete AE dates” (9.2) and “Analysis and Presentation of Adverse Event data from Clinical Trials” (9.6).

7.8.1.4 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.

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.

7.8.1.5 User-defined adverse event category (UDAEC)

UDAEC will be summarized by dose group, primary system organ class and preferred term. In summary, Table 7.8.1.5:1 provides the definition of UDAECs according to AE category or Standardized MedDRA Query (SMQ).

Table 7.8.1.5: 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' 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.

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 = DP + 1/3(SP – DP)) during the episode<70.

The severity of hypotension will be categorised based on the CTCAE grades collected from the eCRF:

- CTCAE grade 1 – mild
- CTCAE grade 2 – moderate
- CTCAE grade 3, 4 or 5 – severe

7.8.2 Laboratory data

The analyses of laboratory parameters will be descriptive in nature and will be based on BI standards (9.7). 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" (9.7). 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 (see Section 6.7) and the last measurement on treatment. Descriptive statistics will be provided by treatment group 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.

Additionally, graphical analysis of the following lab parameters over time until EOS will be performed:

- Haemoglobin
- RBC count / erythrocytes
- WBC count / leukocytes
- Platelet count / thrombocytes
- Reticulocytes
- PT/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 30 days 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 or 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 in order 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 repeated on AST and total bilirubin. 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 analyzed as such.

7.8.3 Vital signs

The analyses of vital signs (blood pressure, pulse rate) will be descriptive in nature. Descriptive statistics of vital signs over time (pre-dose, 1 hour, 2 hours) and for the difference from baseline and pre-dose (see Section 6.7) will be provided by treatment within a study period as described in Table 6.1:1. Figures for change from baseline and change from pre-dose for both 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

A listing for portal vein diameter will be provided.

7.9.2 Biomarker analyses

For all the biomarkers defined in Section 5.4.7, descriptive statistics will be presented.

In detail, for each marker the observed value will be analysed for the BMS via mean, standard deviation, median, Q1, Q3, normalized IQR (0.7413*IQR), minimum, maximum and gMean.

Other exploratory biomarkers may be reported in a separate biomarker report.

7.9.3 PK analyses

Noncompartmental PK parameters will be calculated based on actual sampling times using a validated PK software (Phoenix® WinNonlin® 8.1).

Individual plasma concentration data and the PK parameters calculated thereof will be tabulated and graphically displayed. A patient's PK data will be flagged and excluded from the PK analyses in case of protocol deviations relevant to the evaluation of PK or in case of PK non-evaluability (refer to CTP Section 5.3.1).

7.10 HANDLING OF DMC ANALYSIS

An external data monitoring committee (DMC), independent of the trial and project teams, will be set-up on project level to review all available safety data as well as selected efficacy data in an unblinded manner at regular intervals following first-patient-in. A separate DMC SAP which describes the analyses required for assessment by the DMC will be produced and finalised prior to first patient randomised into the trial. Further details are provided in a DMC charter.

8 TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be released to unblind the trial database after the last patient has completed their End-of-Study/Follow-up visit and all data has been entered and cleaned as defined in the “Data Ready to be Unblinded and / or Final Trial Closure Notification” (RUN) form.

9 REFERENCES

9.1	*CPMP/ICH/363/96*: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9; Note For Guidance on Statistical Principles for Clinical Trials, current version
9.2	*BI-KMED-BDS-HTG-0035:* “Handling of missing and incomplete AE dates”, current version; KMED.
9.3	*KM Asset BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version, KMED.
9.4	*BI-KMED-TMCP-MAN-0012*: “Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics”, current version; KMED.
9.5	*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.
9.6	*KM Asset BI-KMED-BDS-HTG-0066:* “Analysis and Presentation of Adverse Event data from Clinical Trials”, current version, KMED.
9.7	*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	01-JUL-24	[redacted]	None	This is the final TSAP.