# TRIAL STATISTICAL ANALYSIS PLAN

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| **Document No.:** | **c44563547-01** |
| **BI Trial No.:** | 1366-0021 |
| **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<br><br>Including Protocol Revision 6 [c34798591-07] |
| **Investigational Product:** | Avenciguat |
| **Responsible trial statistician:** | [redacted]<br>Tel.: [redacted]<br>Fax: [redacted] |
| **Date of statistical analysis plan:** | 12 July 2024 |
| **Version:** | 1.0 |



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# 1. TABLE OF CONTENTS

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# LIST OF TABLES

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# 2. LIST OF ABBREVIATIONS

| Term | Definition / description |
|---|---|
| AC | Adjudication Committee |
| 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 |
| BIcMQ | BI-customized MedDRA query |
| BLQ | Below Limit of Quantification |
| BMI | Body mass index |
| BMS | Biomarker Set |
| CI | Confidence Interval |
| [redacted] | |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTP | Clinical Trial Protocol |
| CTR | Clinical Trial Report |
| DBL | Database Lock |
| DILI | Drug-Induced Liver Injury |
| DMC | Data Monitoring Committee |
| DBP | Diastolic blood pressure |
| DV | Protocol Deviation |
| ECG | Electrocardiogram |
| EDMS | Electronic Document Management System |
| EoS | End of Study (corresponds with End of Trial) |
| EoT | End of Treatment |
| [redacted] | |
| FAS | Full Analysis Set |
| [redacted] | |
| FHVP | Free hepatic venous pressure |

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| Term | Definition / description |
|---|---|
| [redacted] | |
| HE | Hepatic Encephalopathy |
| HVPG | Hepatic Venous Pressure Gradient |
| ICE | Intercurrent Event |
| ICH | International Council on Harmonization |
| IPD | Important protocol deviation |
| TSAP | Trial Statistical Analysis Plan |
| LLOQ | Lower limit of quantification |
| MedDRA | Medical Dictionary for Drug Regulatory Activities |
| MMRM | Mixed Model with Repeated Measurements |
| NSBB | Non-Selective Beta-Blocker |
| PD | Protocol deviation |
| PEth | Phosphatidylethanol |
| PK | Pharmacokinetic |
| PT | Preferred term |
| REP | Residual effect period |
| RPM | Report planning meeting |
| RS | Randomized Set |
| SBP | Systolic blood pressure |
| SAE | Serious Adverse Event |
| SD | Standard deviation |
| SDL | Subject data listing |
| SMQ | Standardized MedDRA query |
| SOC | System Organ Class |
| TMF | Trial Master File |
| TOC | Table of contents |
| TS | Treated Set |
| ULN | Upper Limit of Normal |
| ULOQ | Upper limit of quantification |
| VH | Variceal Haemorrhage |
| WHVP | Wedged Hepatic Venous Pressure |

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# 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 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, randomisation.

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).[redacted].

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# 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

## 5.1 PRIMARY ENDPOINT

The primary endpoint is defined as the percentage change from baseline in HVPG after 24 weeks of treatment.

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

Either the average FHVP 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 average FHVP, then:

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

if the average FHVP 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 in to optimal, sub-optimal and not evaluable based on the judgement of the central reader. A frequency table of the number and percent of HVPG tracings (measured at baseline, week 8 and week 24) belonging to different quality categories will be provided.

## 5.2 SECONDARY ENDPOINTS

### 5.2.1 Key secondary endpoints

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

### 5.2.2 Secondary endpoints

The following secondary endpoints will be analysed:

- Percentage change in HVPG from baseline (measured in mmHg) after 8 weeks of treatment.

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

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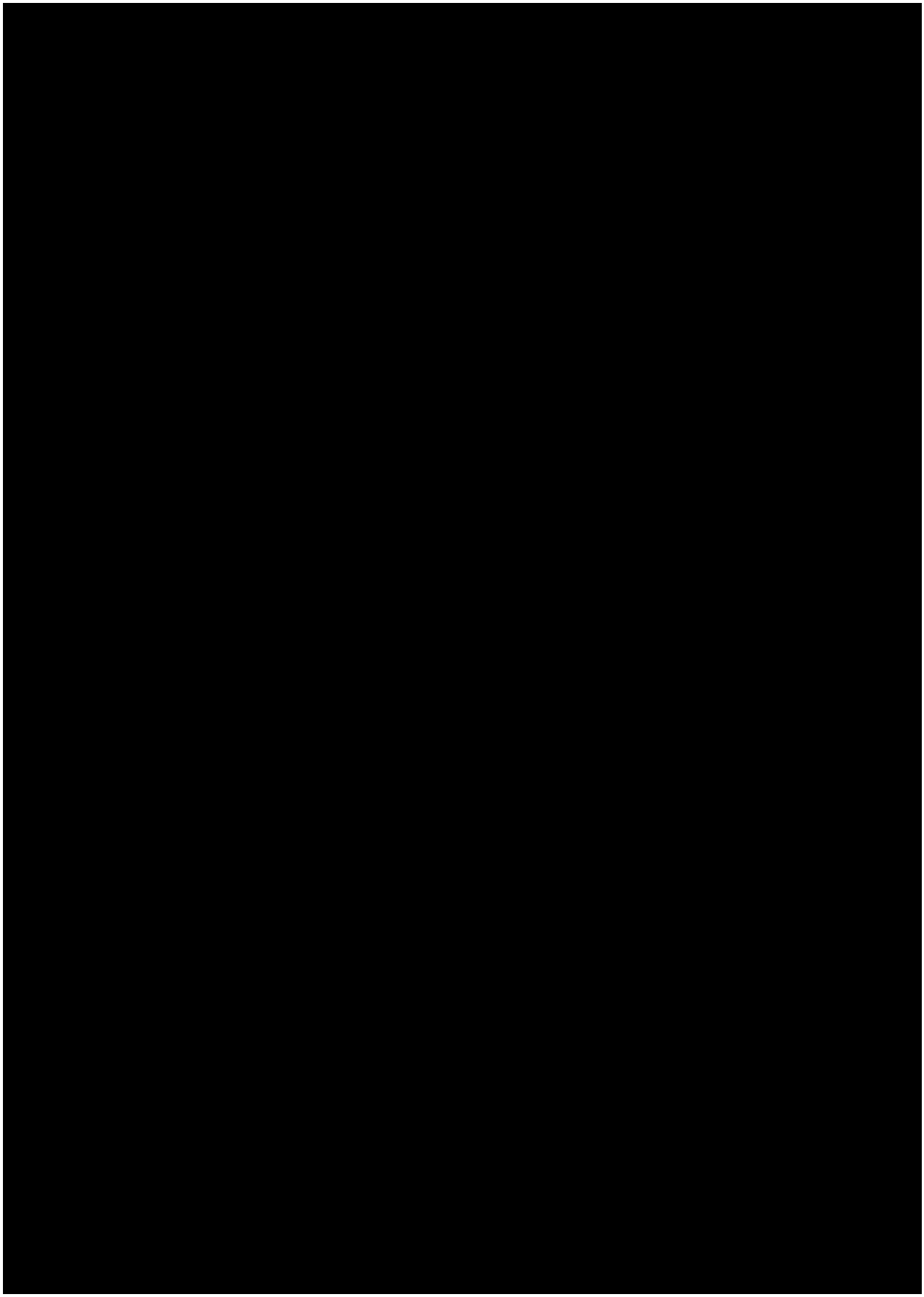

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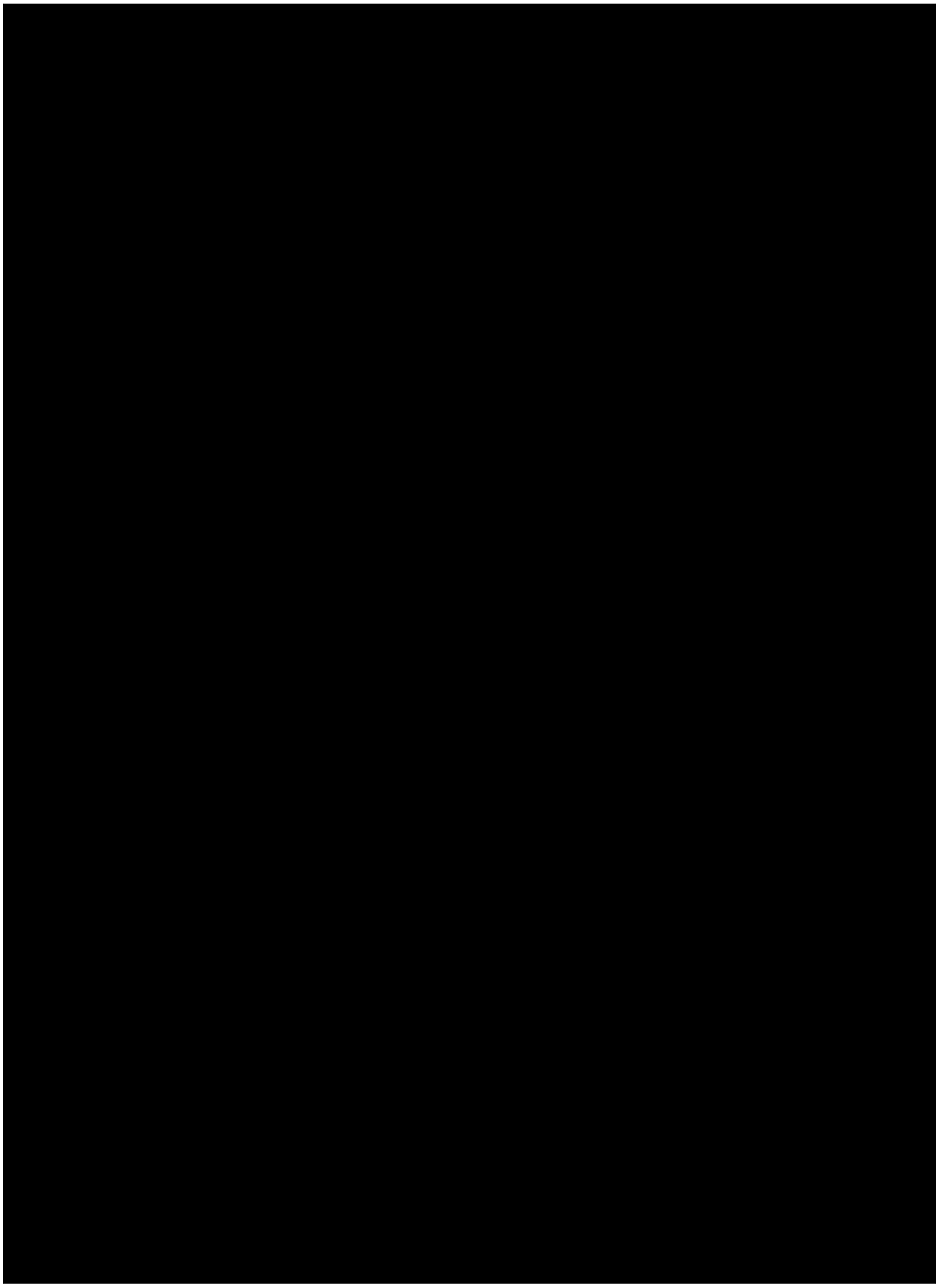

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# 6. GENERAL ANALYSIS DEFINITIONS

## 6.1 TREATMENT

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

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

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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 double-blind study medication - 1 |
| Placebo/ Avenciguat 2mg/ 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. Follow-up phase might not be displayed, e.g., if the patient's trial termination date is within 7 days after last administration of study drug.

For efficacy analyses of HVPG, data up to 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 randomized to.

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

## 6.2 IMPORTANT PROTOCOL DEVIATIONS

Protocol deviations (PD) 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 PD could generate exclusion from analysis sets will be taken during the study and finalized at the last report planning meeting (RPM), i.e., before unblinding.

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

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## 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,
- Occurrence of a decompensation event
- Premature discontinuation of assigned trial medication.

The identified ICEs based on medical review will be confirmed before the DBL.

As a **primary estimand**, the **Hypothetical strategy** will be used for handling these intercurrent events for primary objective as a main analysis as if all the intercurrent events had not happened.

[redacted]

## 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). [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]
- [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 the DBLM.

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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 | RS | TS | FAS | [redacted] |
| Disposition | X | | | | |
| Primary endpoint | | | | X | |
| Secondary efficacy and [redacted] | | | | X | |
| Secondary and further safety endpoints (including liver decompensation) & treatment exposure | | | X | | |
| Demographic/baseline endpoints | | X | | | |
| [redacted] | | | | | |

**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 randomised treatment group. In the case of stratification error at randomisation, the subjects will be analysed according to the stratum to which they actually belong (regardless of any mis-assignment to treatment based on identification of the wrong stratum from IRT), as such an error occurs before randomization and is therefore consistent with regulatory guidance.

Then, for safety analyses, the following will be used in addition:

- If a patient is planned to receive avenciguat (i.e., randomised to either avenciguat 2 mg BID or avenciguat 3 mg BID), then patients will be reported under the planned treatment from the randomization 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

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avenciguat kits at any visit. If the patient was administered at least one kit of avenciguat during the treatment period, then the patient will be assigned to a relevant avenciguat dose treatment group (either avenciguat [redacted] BID or avenciguat [redacted] BID, depending on the kit administered).

[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 Boehringer Ingelheim standards (2).

If the date of first drug administration is missing but the patient was randomized, the date of the first drug administration will be set to the date of randomization. If the date of first administration is partially missing with the month and year present, the day will be set to the date of randomization if randomisation was in the same month. If randomization 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 31$^{st}$ of December of the year (or to the patient’s trial completion date if it is earlier than 31$^{st}$ 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 1$^{st}$ January of the year.

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

### 6.6.6 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 be calculated as if diagnosed on the 15th of that month.

## 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 randomized study medication.

Measurements taken prior to the first intake of randomized 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 6.1:1 below and will be assigned to the randomized study medication for efficacy analyses and to the first study medication taken for safety analyses.

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

Table 6.7:1 Endpoint 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 |
| [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.

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).

For the analyses of the secondary and further safety endpoints at week 8, the actual V7 date + X days (X=3 or 7 days for safety laboratory and AE respectively) will be used for the analysis time windows.

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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[A] (extended) * |
| V1 | Screening | -42 | +7 | | | -∞ | 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 | Day 57 | ±3 | 54 | 60 | 51 | 71 |
| V8 | Week 12 | Day 85 | ±5 | 80 | 90 | 72 | 99 |
| V9 | Week 16 | Day 113 | ±5 | 108 | 118 | 100 | 127 |
| V10 | Week 20 | Day 141 | ±5 | 136 | 146 | 128 | 155 |
| V11 | Week 24/ EoT | Day 169 | ±5 | 164 | 174 | 156 | Study medication stop date + X# days |
| | | | **Off-treatment** | | | | |
| V12 | Week 28/ EoS | Day 197 | ±5 | 192 | 202 | Study medication stop date + X# days +1 | Day of last follow-up value |

[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.

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 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

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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 randomization 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, randomized, screened but not randomized, randomised and treated, randomized but not treated, who completed the treatment period as planned, who were prematurely discontinued study treatment by reason, who is still ongoing in the study, who completed the observational period as planned, who prematurely discontinued study participation, and who completed Week 8 visit (V7).

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 in-text tables presenting descriptive analysis of the endpoints and other variables (in original scale), the set of summary statistics is: N (number of patients with non-missing values), mean, standard deviation (SD).

For end-of-text tables, the set of summary statistics is: 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" (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.

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[redacted]

## 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 based on the RS. A separate listing will be provided for gastroscopy data.

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.

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Table 7.1: 1 Categories for summary of continuous variables

| Variable | Categories |
|---|---|
| Age<br>(years) | < 50<br>50 to < 65<br>65 to ≤ 75<br>> 75<br><br>< 65<br>≥ 65 |
| Weight<br>(kg) | ≤ 70<br>> 70 to ≤ 80<br>> 80 to ≤ 90<br>> 90 |
| BMI<br>($kg/m^2$) | < 25<br>25 to < 30<br>≥ 30 |
| eGFR | ≤ 30<br>> 30 to ≤ 45<br>> 45 to ≤ 60<br>> 60 to ≤ 90<br>> 90 |
| Time since first diagnosis of cirrhosis<br>(years) | ≤ 1<br>> 1 to ≤ 5<br>> 5 to ≤ 10<br>> 10 |
| Baseline HVPG<br>(mmHg) | ≤ 12<br>>12<br><br>≤ 15<br>>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 Organization – Drug Dictionary (WHO-DD).

A medication will be considered concomitant to treatment if it:

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- 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 summarized 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:

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

## 7.4 PRIMARY OBJECTIVE ANALYSIS

### 7.4.1 Main analysis

The primary endpoint will be analysed through a MMRM model in combination with the primary estimand of handling ICEs (see Section 6.3). The FAS will be used for the analysis: the patient set includes all patients who had at least one evaluable baseline HVPG measurement. The missing data will not be imputed. Instead, the MMRM will handle missing data based on a likelihood method under the "missing at random" assumption.

For the MMRM model, treatment at each visit, use of NSBBs or carvedilol (yes / no) at baseline, and baseline HVPG at each visit will be used as covariates. Refer to Section 7.2.3 of the CTP for a detailed description of the statistical analysis for the percentage change from baseline in HVPG after 24 weeks of trial treatment.

The adjusted estimate of mean percentage change from baseline in HVPG at 24 weeks and its standard error will be obtained from MMRM for the placebo and treatment groups. The 95% CI will be provided for adjusted mean effect of each treatment group as well as the comparison with placebo.

SAS code for **the MMRM model** will be based on the following structure:

```
PROC MIXED DATA=alldat cl method=reml;

CLASS visit trt subject;

MODEL chg = base*visit visit*trt stra / ddfm=kr s CL; REPEATED visit / subject=
subject type=un r rcorr;
```

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```
LSMEANS visit*trt /pdiff=all om cl alpha=0.05 slice=visit;

RUN;
```

## 7.5 SECONDARY OBJECTIVE ANALYSIS

### 7.5.1 Key secondary objective analysis

This section is not applicable as no key secondary endpoints have been specified in the protocol.

### 7.5.2 Secondary objective analysis

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

For the secondary endpoint of percentage change in HVPG after 8 weeks of treatment, the analysis of covariance (ANCOVA) will be used. The analysis will be performed on the FAS with treatment assignment as randomized and include on-treatment HVPG only. If a patient misses the Week 8 visit, the missing data will not be imputed.

This model will include treatment and use (or not) of NSBBs or carvedilol 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 $\sigma^2$. The analysis will only be used for estimation of treatment effects without performing statistical tests.

For other secondary endpoints, only descriptive statistics will be presented.

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

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## 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 (in years) that all patients pooled together were on treatment. A separate listing will be created for patients who switched treatment at any time (i.e., down-titration) 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, >8 to 12 weeks, >12 to 18 weeks, >18 to 24 weeks, >24 weeks.

No temporary treatment interruption period will be reported.

## 7.8 SAFETY ANALYSIS

AEs reported to be related to study procedures will be based on the enrolled set and listed. All the other safety analyses will be performed based on the TS following BI standards.

### 7.8.1 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 (randomization 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. For this purpose, AE data will be combined in a 2-step procedure into AE records.

In the first step, AE occurrences, i.e., AE entries on the CRF, will be collapsed into AE episodes if all of the following apply:

- The same MedDRA lowest level term was reported for the occurrences.
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence.
- Treatment did not change between the onset of the occurrences OR treatment changed between the onset of the occurrences, but no deterioration was observed for the later occurrence.

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In a second step, AE episodes will be condensed into AE records provided that the episodes were reported with the same term on the respective MedDRA level and that the episodes are assigned to the same treatment.

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 until 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.

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 2 mg and avenciguat 3 mg), 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 summarized 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’.

7.8.1.3 AE summaries

An overall summary of AEs will be presented.

The frequency of patients with AEs will be summarized by treatment, primary SOC and PT. AEs which were defined as secondary endpoints will be summarized 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 dose reduction, for patients with AEs leading to discontinuation, and for patients with drug-related AEs.

The SOC will be sorted alphabetically, PTs will be sorted by frequency (within SOC). Customized sorting orders may also be used based on trial needs, e.g., SOC sorted by frequency.

For further details on summarization 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).

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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 randomization 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.

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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 $\left(\frac{\text{lowest SBP during the episode – baseline SBP}}{\text{baseline SBP}}\right) \geq 30\%$;
- Baseline SBP >140: decrease $\left(\frac{\text{lowest SBP during the episode – baseline SBP}}{\text{baseline SBP}}\right) \geq 40\%$;
- Or lowest SBP during the episode <90.
- Baseline DBP <=70: $\left(\frac{\text{lowest DBP during the episode – baseline DBP}}{\text{baseline DBP}}\right) \geq 30\%$;
- Baseline DBP > 70: $\left(\frac{\text{lowest DBP during the episode – baseline DBP}}{\text{baseline SBP}}\right) \geq 40\%$;
- 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 (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 (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.

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.

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The following lab parameters will also be presented graphically:

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

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 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 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 analysed 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 during treatment period and post-treatment period (pre-dose, 1 hour, 2 hours) and for the difference from baseline and pre-dose (see Section 6.7) will be provided by treatment Figures for change from baseline and change from pre-dose for both on-treatment visit and post-treatment visit will be provided as well.

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### 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.

### 7.8.5 Ultrasound

Descriptive analysis of change from baseline of portal vein diameter at week 8 and week 24 will be provided. A listing of all the collected data from the ultrasound CRF page for each patient will be reported.

# 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 EoS/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.

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# 9. REFERENCES


| | |
|---|---|
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| 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 |

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# 11. HISTORY TABLE

Table 11: 1 History table

| Version | Date (DD-MMM-YY) | Author | Sections changed | Brief description of change |
|---|---|---|---|---|
| 1.0 | **12-July-24** | [redacted] | None | This is the final TSAP |