Sponsor: AOP Orphan Pharmaceuticals AG
Protocol: LDLL300.401
EudraCT number: 2017-002138-22

Phase IV, multicenter, prospective, randomized, open-label, controlled study on Landiolol in patients with septic shock resident in an Intensive Care Unit (LANDI-SEP)

STATISTICAL ANALYSIS PLAN

VERSION: Final 1.0
DATE: 27-APR-2022

Signatures:

ANOVA CRO: Marie Šimečková (Project Statistician)

Signature: _____ Date: _____

AOP Orphan Pharmaceuticals AG: Christoph Klade (Chief Scientific Officer)

Signature: _____ Date: _____

Martin Unger (Head of Clinical Development)

Signature: _____ Date: _____

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
ATC	Anatomic, Therapeutic, Chemical (Classification System for Drugs)
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organisation
CSR	Clinical Study Report
DB	Database
DBD	Diastolic Blood Pressure
FAS	Full Analysis Set
GEE	Generalized Estimating Equations
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference of Harmonization
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
ITT	Intent-To-Treat
IU	International Unit
MAP	Mean Arterial Pressure
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model with Repeated Measures
NA	Not Applicable, Not Available
PPS	Per-Protocol Set
PT	Preferred Term
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Systems
SBD	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
TFL	Tables, Figures and Listings
VIS	Vasoactive-inotropic score

INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical analyses to be performed on the study, contains the definition of analysis sets and protocol deviations, specifies the primary and secondary endpoints and outlines the tables, listings, and figures (TFL).

The analysis of the pharmacokinetics data will be described in a separate SAP.

This analysis plan is based on the versions of Study Protocol dated 15-DEC-2020, and e-CRF MSU 10, signed 05-OCT-2020, respectively. The analyses and TFL closely follow the ICH guidelines for industry on topic E3 (Structure and Content of Clinical Study Reports) [1] and E9 (Statistical Principles for Clinical Trials) [2].

The SAP must be finalized and approved before the database (DB) lock and executed after the DB lock. Protocol deviations must be defined and subjects' disposition into analysis sets should be approved before the DB lock.

1 PLANNED CHANGES FROM STUDY PROTOCOL

The definition of the primary endpoint was specified in more details by sponsor.

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE(S)

The primary objective is to compare the rate of patients with heart rate response and maintenance thereof without increase in vasopressor requirements in the first 24 hours after treatment start in a septic shock population with persistent tachycardia (≥95bpm), randomized to either standard treatment and continuous LDLL300 infusion (Group L) or standard treatment only (Group C).

2.2 SECONDARY OBJECTIVE(S)

To further assess efficacy and safety in the two treatment arms.

3 STUDY DESIGN

3.1 BRIEF DESCRIPTION OF STUDY DESIGN

This is a multicentre, randomized, controlled, open-label phase IV trial in patients with septic shock and persistent tachycardia/tachyarrhythmia (HR ≥95 bpm) treated with LDLL300 in addition to standard treatment vs. standard treatment alone (i.e., no treatment with β-blockers).

Patients with septic shock resident in the Intensive care unit (ICU), who after having completed the haemodynamic optimization phase (at least 12 hours but a maximum of 36 hours after resuscitation according SSCG 2016 guidelines), still have tachycardia and/or tachyarrhythmia with HR ≥95 bpm will be assessed by applying the selection (inclusion/exclusion) criteria mentioned in Sections 10.1 and 10.2.

A total of 200 Patients who fulfil all the selection (inclusion/exclusion) criteria has been randomized 1:1 to one of the two treatment groups (Group L or Group C).

The subject's participation will be a maximum of 28 days (starting from the day of randomization until Day 28).

3.2 RANDOMIZATION

Randomization should be performed immediately after eligibility confirmation and Informed consent form (ICF) signature (signed by the patient or a legal representative or other country-specific documentation, as required). Patients have been randomized to either Group L or Group C. Presence of atrial fibrillation during the haemodynamic optimization period was used as the stratification factor.

4 STUDY ENDPOINTS

4.1 PRIMARY ENDPOINT

- Heart rate response and maintenance thereof and no increase in vasopressor requirements in the first 24 hours after treatment start

4.2 SECONDARY ENDPOINTS

- Change in vasopressor requirements over the study period (dose and duration)
- Daily inotropic requirements (as long as the patient is treated with vasopressors)
- Heart rate response during the first 24 hours after treatment start
- 28-day mortality (all cause)
- ICU mortality (all cause)
- Duration of ICU stay (survivors/non-survivors)
- Duration of hospital stay (survivors/non-survivors)
- SOFA score (as long as the patient is treated with vasopressors) on Day 1, 2, 3, 4, 7, 10, 13, 16, 19, 22, 25 and 28

4.3 SAFETY ENDPOINTS

- Incidence rate of bradycardic episodes requiring intervention
- Incidence of Adverse Events (AE)
- Incidence of Serious Adverse Events (SAE)
- Incidence of new onset arrhythmia
- Other safety endpoints (laboratory measurements, haemodynamic parameters, and physical examination)

5 DEFINITIONS

5.1 STUDY DATABASE AND EXTERNAL DATA

Data collected and validated in the clinical study database will be analysed. The pharmacokinetics data will be provided in an external excel-file from the laboratory and imported into SAS [3].

5.2 LABELS USED IN SAP AND IN STATISTICAL OUTPUTS

5.2.1 Treatment arms

The treatment arms will be labelled as Group L (standard treatment and continuous LDLL300 infusion) and Group C (standard treatment only).

5.2.2 Stratification groups

The presence of atrial fibrillation in the haemodynamic optimization period is the stratification factor for randomization and will be also used as stratification factor in all analyses.

For some patients, the presence of atrial fibrillation was reconsidered after the randomization. The corrected value will be used for analyses.

5.2.3 Study visits/ time-points

Both study groups will undergo the following visits:

- **Eligibility visit:** Patients in the ICU will be screened for eligibility. Patients who fulfil all the inclusion criteria and none of the exclusion criteria will be eligible to participate in the study.
- **Randomization (V-R):** Randomization should be performed immediately after eligibility confirmation and ICF signature. Patients will be randomized to either Group L or Group C.
- **Baseline visit (V0)**: 0 – 2h after the randomization (V-R) and before the treatment start.
  Medical history, demographics, APACHE II Score, solicited concomitant medication, basic haemodynamic parameters, physical examination, cardiac rhythm assessment, clinical laboratory, blood gas analysis, SOFA Score and daily fluid are assessed.

  In patients with an in-situ Swan Ganz (CO, CI, MPAP, PAOP) or PICCO/FloTrac (CO, CI, GEDI, ELWI) catheter haemodynamic parameters should be documented. Echocardiographic evaluation of cardiac status is mandatory before treatment start, assessments made within 2 hours prior Randomization shall be accepted. If performed as routine assessment, haemodynamic parameters (LVEF, SV, TAPSE, VTI) measured via cardiac echo should also be documented.
- **TREATMENT PHASE (V1-V28)**

  The Treatment Phase starts with the beginning of Titration Phase.

  Adverse events and solicited concomitant medication (vasopressors and inotropes) are documented over the entire study period. Other concomitant medication and treatments are documented until End of Vasopressor Treatment Visit (EOvT).

  For Group L, LDLL300 infusion rate and dosage must be documented in detail over the entire study period.

  - **Titration Phase (V1):** 0 – 24 h

    The Titration Phase begins with the start of LDLL300 administration in Group L or 2 hours after the randomization in Group C, which is the time 0.

    During the Titration Phase, basic haemodynamic parameters should be documented at treatment start and every subsequent hour until Hour 24 after treatment start. For Group L, these parameters are also be documented for every LDLL300 dosing change. Body temperature is documented every 12 hours. Solicited concomitant medication (vasopressors and inotropes) should be documented in detail (every dose change).

    SOFA Score, clinical laboratory, blood gas analysis should be assessed during the visit 24-hour-fluid balance (In/Out) should be assessed. Reference start point is the end of Baseline Visit fluid assessment time.

    In patients with an in-situ Swan Ganz (CO, CI, MPAP, PAOP) or PICCO/FloTrac (CO, CI, GEDI, ELWI) catheter haemodynamic parameters should be documented. If performed as routine assessment haemodynamic parameters (LVEF, SV, TAPSE, VTI) measured via cardiac echo should also be documented.

    Assessments should be performed within a timeframe of ± 30 minutes of their respective starting time. LDLL300 dose change parameters must be assessed at dose change timepoint.
  - **Maintenance Phase I (V2-V4):** 48h, 72h, and 96h

    During Maintenance Phase I, basic haemodynamic parameters should be documented every 12 hours for both study groups and additionally at every LDLL300 dosing change for Group L. Body temperature should be documented every 12 hours. Solicited concomitant medication should be documented as daily dose.

    SOFA Score, clinical laboratory, blood gas analysis should be assessed daily. 24-hour fluid balance (In/Out) should be documented. Daily 24h Fluid balance (In/Out) should be assessed continuously following V1.

In patients with an in-situ Swan Ganz (CO, CI, MPAP, PAOP) or PICCO/FloTrac (CO, CI, GEDI, ELWI) catheter haemodynamic parameters should be documented. If performed as routine assessment haemodynamic parameters (LVEF, SV, TAPSE, VTI) measured via cardiac echo should also be documented.

Assessments with specific timepoints (i.e. haemodynamic parameters, body temperature) should be performed within a timeframe of ± 6 hours of their respective starting time. LDLL300 dose change parameters must be assessed at dose change timepoint.

- **Maintenance Phase II (V5-V28):** Day 5 – Day 28

  During Maintenance Phase II, basic haemodynamic parameters should be documented every 12 hours for both study groups and additionally at every LDLL300 dosing change for Group L. Body temperature should be documented every 12 hours. Solicited concomitant medication should be documented as daily dose.

  SOFA Score should be assessed on Day 7, 10, 13, 16, 19, 22, 25 and 28 (V7, V10, V13, V16, V19, V22, V25, V28).

  Assessments with specific timepoints (i.e. haemodynamic parameters, body temperature) should be performed within a timeframe of ± 6 hours of their respective starting time. LDLL300 dose change parameters should be assessed at dose change timepoint.

- **End Of Vasopressor Treatment (EOvT):**

  End of Vasopressor Treatment is achieved if all vasopressors have been discontinued and the investigator does not expect their re-initiation, if patient dies, or at Day 28. Reason for EOvT, AEs, concomitant medication and treatments should be documented. In case of study withdrawal, status of vasopressor treatment at time of withdrawal is documented.

- **Day 28 Follow-Up (V28):** Day 28

  For the Day 28 Follow-up (V28), the survival of the patient, time of extubating and discharge from ICU and/or hospital should be assessed. In case of discharge from ICU or hospital, the assessment of survival may be done by simple telephone contact with a treating physician or the patient himself. At least three follow-up attempts should be performed and documented.

  At the Investigator´s discretion a pregnancy test may be performed.

- **Unscheduled Visits**

  Additional safety and/or follow up visits might be applicable in case of ongoing or persisting AEs. Any assessments deemed necessary by the Investigator are documented.

5.3 BASELINE VALUES

Baseline value is defined for each parameter as the last value measured before the first study drug administration, i.e., before the start of the titration phase.

Reference point for calculation of daily fluid balance for the last 24 hours is the closest possible timepoint ± 12 h from treatment start timepoint.

Baseline for the vasopressors treatment is the dose of vasopressors at the beginning of the treatment period.

6 ANALYSIS SETS

The following analysis sets are defined in the study protocol (Section 13.2).

6.1 SAFETY SET

Safety Analysis Set (Safety) will include all randomized patients who entered the Treatment Phase.

6.2 FULL ANALYSIS SET (FAS)

Full Analysis Set (FAS), defined as close to the Intention-to-Treat (ITT) principle as possible, will be the primary set used for the efficacy analyses. The FAS will be equal to the Safety, i.e., the FAS will include all randomized patients who entered Treatment Phase regardless of protocol deviations or completion of the study. The analysis using FAS will compare treatment groups as assigned by the randomization.

6.3 PER-PROTOCOL SET (PPS)

Per-Protocol set (PPS) will consist of FAS patients without major protocol deviations which lead to the exclusion from the PPS. The major protocol deviations which lead to the exclusion are defined in the next section.

6.4 PROTOCOL DEVIATIONS

List of protocol deviations (PDs) and their classification as major or minor was discussed on the Data review meeting (DRM) and agreed after. The classification was assigned in eCRF and is present in the PD dataset in the export.

Major protocol deviations which influence the randomization process or the efficacy endpoints will be reasons for exclusion from the Per-Protocol set.

6.4.1 Conditions for major protocol deviations

The major protocol deviation which leads to the exclusion from the PPS include the following:

- Missing haemodynamic assessment during the titration phase.
- Violation of the randomization procedure (i.e. change of the atrial fibrillation yes/no classification after the randomization)
- Violation of eligibility criteria with strong impact on the study conduct (see Table 1)
- Violation of the study medication administration with strong impact on the study conduct (see Table 1)

The major protocol deviation which does not lead to the exclusion from the PPS because there is no impact on the study population, randomization process or efficacy endpoints include the following:

- Errors in the AE/SAE reporting process
- Errors in the informed consent signing process
- Violation of eligibility criteria with no impact on the study conduct (see Table 1)
- Violation of the study medication administration with no impact on the study conduct (see Table 1)

No major deviation in time-scheduled defined in the study protocol was recorded.

Table 1 Classification of major protocol deviations connected to the eligibility criteria and study medication as leading / not leading to exclusion form the analyses set; classification decided on DRM

Patient ID	Deviation type	PD ID	Description	Decision
S07-02	Inclusion/ Exclusion criteria	5	The subject enrolled/screened 26 min after the end of the maximum of stabilization period (up to 36h). As per the SI the subject was classified as eligible within the timeline but enrolled late. The inclusion No. 6 not met.	Exclude

S07-21	Inclusion/ Exclusion criteria	1	Patient received Metoprolol (Betaloc) on 13Jan2021 at 12:30-12:35 after septic shock diagnosis and during stabilization period in purpose to be enrolled in Landisep study - done 14Jan2021 at 10:30.	Exclude
S10-01	Inclusion/ Exclusion criteria	2	Patient 10-01 was found elegible and randomized before the 12-36 hours of the hemodynamic optimization period. The heamodinamic stabilization started on 17MAY209 at 14:00 so 10 hours before the randomization. Inclusion criteria #6 was violated	Exclude
S10-06	Inclusion/ Exclusion criteria	2	Patient S10-06 started Vasopressor infusion on 23-DEC-2020 at 15:00 and the patient has been randomized on 24-DEC-2020 at 00:28 (V1 started at 02:28). Patient S10-06 didn't meet the inclusion criteria n. 6 because the haemodynamic stabilization lastes only 09 hours and 28 minutes instead of 12-36h.	Exclude
S10-09	Inclusion/ Exclusion criteria	1	Noradrenaline infusion started on 18-JAN-2022 at 08:00 while patient S10-09 was randomized in the study on 20-JAN-2022 at 16:13. Haemodynamic stabilization lasted 56 hours and 13 minutes instead of 12-36 hours according to Protocol.	Exclude
S12-08	Inclusion/ Exclusion criteria	3	Patient was randomized after 6 hours of heamodynamic stabilization with vasopressor. The Investigator has considered the haemodynamic optimization performed with fluid in the previous Department in which the patient was hospitalized.	Exclude
S12-11	Inclusion/ Exclusion criteria	1	Inclusion criteria #6 not respected. Patient 12-11 started Noradrenaline infusion on 26FEB2021 at 16:00 and she was randomized on 26FEB21 at 18:39 after only 02:39 hours of haemodynamic stabilization	Exclude
S12-13	Inclusion/ Exclusion criteria	1	Patient S12-13 has been randomized even if exclusion criteria 2 was not met. The root cause analysis conducted with the SI has confirmed that, in order to interrupt the Beta-Blocker (metopropolol), time of randomization was considered instead of the Septic shock diagnosis.	Exclude
S15-02	Inclusion/ Exclusion criteria	5	Exclusion Criteria#2 - ÃŸ-Blocker (Concor) was administered within 72h prior to randomization	Exclude
S16-02	Inclusion/ Exclusion criteria	1	Prohibited medication (Beta blocator) within 72 hr. prior study inclusion.	Exclude
S28-01	Inclusion/ Exclusion criteria	2	Patient S28-01 did not get continuous vasopressor treatment - as it is required according to Inclusion criteria 3c - at the time of eligibility check. Patient has not undergone at least 12 hours continuous vasopressor treatment at the time of enrollment. Patient has received vasopressor for 3h50mins before the treatment started, therefore patient did not comply with Inclusion criteria #6.	Exclude
S03-01	Inclusion/ Exclusion criteria	25	Patient swallowed one Pill of Inderal (Propanolol) (=Beta Blocker) the day before inclusion (exclusion criteria 2 deviation) - patient was included by mistake. This was detected while ConMed entry after patient had completed study already.	Not-exclude
S12-01	Inclusion/ Exclusion criteria	3	According to SD reading, data confirmed that patient S12-01 has been randomized after approximately 16 hours of haemodynamic stabilization instead of the 24-36 hours as per CSP v3.0	Not-exclude
S03-03	Study medication	3	Infusion of landiolol starts by 5 mcg/kg/min - severe tachycardia, no time to titrate every 20 mins	Exclude
S10-01	Study medication	6	The patient's weight was 95Kg, the LDLL300 infusion rate was calculated erroneusly considering the patient 105kg.	Exclude
S15-03	Study medication	2	Because of a calculation error, the initial starting dose of LDLL300 was set too high at 6.05 ug/kg/min instead of 1ug/kg/min and the first dose change was also miscalculated accordingly with 12.09 ug/kg/min instead of 2 ug/kg/min	Exclude
S16-64	Study medication	1	14Jan2022 at 11:23 - The LDLL300 dose was increased earlier, after 14 min from the previous dose change. The minimum dose interval of 20 minutes was not followed.	Not-exclude

S18-01	Study medication	4	First dose increase by 1 ug/kg/min after LDLL300 infusion start on 02-DEC-2018 at 15:06 was not done after 20 minutes, but rather after 7 minutes at 15:13. Subsequently, the 20 minute time interval was also shortened twice by 2 minutes each until target heart rate was reached for the first time at 18:32.	Not-exclude
S18-25	Study medication	1	Patient S18-25 once fell below the minimum duration of 20 min (minimum dose interval) in the titration phase (on 21Jul2020 19:02 - 19:18). The clock in the patient's room shows a different time than in the electronic file.	Not-exclude
S18-30	Study medication	1	Vial No. 4573, 10.06.2021 Start 19:15: The high titration from 12,00 mcg/kg/min to 13,00 mcg/kg/min was one minute too early.	Not-exclude

Other PDs are considered minor.

6.5 SUBGROUPS

Subgroup analyses will have exploratory character. The primary and secondary efficacy endpoints will be analysed by the following subgroups and presented in the same way as the overall results:

- Heart rate at baseline (≤120 / >120)
- Stratification factor: Presence of Atrial fibrillation at baseline (Yes / No)
- Norepinephrine equivalent score (Goradia [4], see Section 7.3.2) at the beginning of treatment period (≤0.3 / >0.3)
- Any concomitant antiarrhythmic agents during the titration phase (Yes / No)
  The antiarrhythmic agents are identified by the ATC codes C01AA, C01BC, C01BD, C07AB, C08DA, or preferred codes 00090101001, 05513502001.
- Primary endpoint response (Responder / Non-responder) will be performed for secondary endpoints only.
- Covid 19 ongoing at the beginning of the treatment phase (Yes / No)
  Covid 19 infection is defined by HLT (HLT = Coronavirus infections).
- Heart rate endpoint response (Responder / Non-responder) will be performed for secondary endpoints only.
- Gender (Male/Female)

The following subgroups analyses can be performed post-hoc:

- Beta blocker in the medical history (Yes / No)
  The beta blockers are identified by the ATC4 code C07A.
- Administration of Vasopressin (Yes / No)
- Administration of Dobutamine (Yes / No)
- Administration of Simdax (preferred code 01538201001) (Yes / No).
- Renally impaired at baseline (eGFR <45ml/min)

The details will be specified post-hoc.

The subgroups analyses will be done on FAS.

7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This section describes the data analysis in detail. The statistical methods are planned in accordance with the study protocol (Section 13) and in accordance with ICH Topic E9 Statistical Principles for Clinical Trials.

7.1 GENERAL PRINCIPLES

Statistical software SAS (version 9.4 or higher) will be used for the analysis and for generation of TFL.

The analyses will be performed using standard level of significance 5%. Two-sided 95% confidence intervals and two-sided statistical tests are planned to be used for the comparison of treatment groups.

7.1.1 Descriptive statistics

For categorical data, standard set of summary statistics will be counts and percentages.

For continuous data, the following descriptive statistics will be presented: number of available observations, number of missing observations, mean, standard deviation (SD), median, lower quartile, upper quartile, minimum, and maximum.

When appropriate, results will be presented by treatment groups as well as overall.

If needed, results will be presented by different patient characteristics, such as sex or age group, as well as overall. Figures used to illustrate selected summary tables will always refer to the number of patients included in the analysis set.

7.1.2 Rounding procedures

The following rounding procedures will be used:

- Min, Max: same number of decimal places as the original value.
- Mean, median and its confidence intervals, Q1, Q3: one more decimal place than the original value.
- SD: two more decimal places than the original value.
- Percentages:
    - Safety variables: one decimal place.
    - Efficacy variables: two decimal places.
    - In case the percentages are very close to 0 or 100: more decimal places can be used.

7.1.3 Unscheduled/ repeated assessments

Unscheduled or repeated assessments will be listed only; they will be considered for the baseline values evaluation.

7.1.4 Missing data

Missing data includes missing assessments as well as the data missing due to premature termination.

Handling of missing data for evaluation of primary endpoint is described in Section 7.3.2 Primary analysis. In secondary analyses, statistical methods which consider presence of missing data (longitudinal analyses with repeated measures, censoring) will be used; therefore, imputation of missing data is not planned.

7.1.5 Methods for handling of incomplete dates/times

For calculation of AEs treatment duration, identification of treatment emergent AE, time of septic shock diagnosis, and prior / concomitant medication, incomplete date and times will be imputed as follows:

- Dates of start: Start date of AEs/MH will be imputed by date of the first day in corresponding month or year and start time will be imputed by midnight time (00:00). If the AE started on day of the start of the treatment period, the start time will be imputed as the start of the treatment.
- Dates of end: End dates of AEs/MH will be imputed by date of the last day in corresponding month or year and end time will be imputed by time 23:59. If the patient died and the end date is completed as unknown then the end date is imputed as date of death.

When the day of end of a medication in CM dataset is unknown, we assume it is a prior medication; when the medication ended on day of the treatment period start and its time is unknown, we assume it to be concomitant medication.

Because the time of the visits in Maintenance Phase I and II has not been recorded, it is imputed by the time of visit V1 (start of the treatment period).

7.1.6 Outliers

Because the primary endpoint is a dichotomized variable, there are no outliers.

It is unlikely that a strong outlier will occur for a secondary endpoint because of their characteristics. However, in such case, a post-hoc exploratory sensitivity analyses with exclusion of this observation could be done.

7.1.7 Validation of statistical programming

The analyses of the primary endpoint and adverse events will be double programmed by the second statistician and the results will be checked. Disposition of subjects will be checked by the second statistician.

Other outputs will be reviewed by the second statistician. Logs of all programs used for analysis and data preparation will be checked for errors and unexpected warnings.

Any undocumented updating of study data in statistical programs instead of change in clinical DB (or source data) is not allowed. Specifically, this refers to the cases where subjects or the data are added/ changed using a statistical program rather than updating the DB. This kind of hard coding is usually proposed to correct deficiencies (missing values, wrong values, and wrong measurement units) in the DB when these errors are detected after DB lock.

No hard coding is done in any programs used for the creation of analysis data sets, tables, listings, or analyses that are intended for external reporting after DB lock (i.e., clinical study reports, publications, abstracts, etc.).

This policy ensures integrity of clinical data, since no changes are made to the study data without appropriate documentation from the investigator sites and appropriate audit trails within the clinical trial DB.

7.2 DESCRIPTION OF BASELINE CHARACTERISTICS

7.2.1 Disposition of patients

The number and percentage of screened, randomized, and treated patients, number of premature discontinued patients (together with the reason for discontinuation) and patients who completed the study will be presented by treatment arms and overall. Also, number of patients in the Safety set, FAS and PPS will be presented.

Disposition of patients by visits and duration of the stay in the study will be presented.

Frequencies of patients by countries and sites will be presented.

7.2.2 Protocol deviations

Major protocol deviations as well as major protocol deviations leading to exclusion from PPS will be analysed. The number of protocol deviations and the number and percentage of patients with protocol deviations will be presented.

7.2.3 Description of baseline characteristics

The following baseline characteristics will be analysed using the standard sets of summary statistics as defined in Section 7.1:

- Demographics: age, gender, and ethnicity

- Presence of atrial fibrillation in the haemodynamic optimization period (stratification factor)
- APACHE II Score
- SOFA Score
- Norepinephrine equivalents score (Goradia [4], see Section 7.3.2) at the beginning of the titration phase (0h)
- Basic haemodynamic parameters: Mean arterial pressure (MAP), systolic arterial pressure (SAP) and diastolic blood pressure (DAP) in mmHg, Heart rate (HR) in bpm,
- Cardiac rhythm assessment at baseline
- Time since the septic shock diagnosis to the beginning of the treatment phase
- Mechanical ventilation at baseline
- Renal replacement therapy at baseline
- Physical examinations: Weight (kg), height (cm) and BMI (kg/m2), body temperature (°C)
- Left ventricular ejection fraction at baseline
- Arterial lactate level, Arterial pH
- Site of infection: respiratory, abdominal, urinary tract, surgical, other

Baseline characteristics will be compared between treatment groups using standard statistical tests depending on distribution of the data (two-sample t-test, two-sample Welsh's test, two-sample Wilcoxon test, Fisher test, Chi-square test). This is a randomized study; therefore, difference between treatment groups in baseline characteristics is only matter of chance (and due to multiple testing probability of false positive results of statistical tests will be higher than 5%). If statistically significant difference between treatment groups is identified, it will be commented in the statistical report.

Further, it will be decided whether the characteristic showing (statistically or clinically) significant difference between treatment groups will be added into model as covariate for the purpose of sensitivity analysis to explore effect of this misbalance to study results. If no statistically significant difference in baseline characteristics will be identified, it will be stated in the statistical report.

The medical history, prior medication, prior treatment, concomitant medication, and concomitant treatment will be summarized. The prior medication/treatment is the medication/treatment which ended before the start of the treatment phase; concomitant medication/treatment is the medication/treatment used in the treatment period (regardless the start date/time). The medication will be coded by WHODrug Global B3 March 1, 2022.

7.3 ANALYSES OF EFFICACY

7.3.1 Exposure to study drug

The total duration of the Landiolol treatment (difference between the start of the treatment and the end of the last landiolol administration) and the length of Landiolol infusion (the time when Landiolol treatment was suspended excluded) will be summarized.

The total amount of administered Landiolol and the average dosage per kg and min in the titration phase, in the Maintenance Phase I, Maintenance Phase II and during the whole study will be summarized. The boxplot (including median and quartiles) of the dosage in the titration phase and during the whole study will be plotted.

7.3.2 Primary analysis

Absolute and relative frequencies of patients who achieved the primary endpoint (responders) will be calculated. A patient is a responder when the following two conditions are fulfilled:

1. Heart Rate responder: The target heart rate is achieved and maintained during the Titration Phase.

   The target heart rate is **achieved** when three subsequent values of heart rate are either in the interval 80 – 94 bpm (regardless clinical significance) or under 80 bpm and not clinically significant. The heart rate measurements at the beginning (0h) and end (24h) of the titration phase are not considered.

   The target heart rate is not **maintained** when three subsequent values are higher than 94 bpm, or three subsequent clinically significant values are lower than 80 bpm after the first achievement of the target. The heart rate measurement at the beginning (0h) of the titration phase are not considered.

   For patients who ended the vasopressor treatment during the first 24 hours after the start of the treatment period only the heart rate values measured before the end of vasopressor treatment are used for the evaluation of the response.

   Patients who discontinued the study during the first 24 hours after the start of the treatment period are assumed to be non-responders.

   When a measurement of heart rate is missing at some timepoint (because of other reasons than discontinuation of the study or end of vasopressor treatment), we assume the "worst case scenario", i.e., the target heart rate value is not reached.

   Only the heart rate results measured regularly as the physical examination will be used in the Group L (heart rate values recorded at the time of change of Landiolol dose will not be considered) to have comparable results in both groups.

2. Vasopressor responder: The Norepinephrine equivalents score (Goradia [4]) at the beginning of the treatment phase is higher than or equal to the value of the score at 24 hours after the treatment phase start.

   The Norepinephrine equivalents score (Goradia [4]) is defined as follows:

   NE = norepinephrine [mcg/kg/min] + epinephrine [mcg/kg/min] + phenylephrine [mcg/kg/min]/10 + dopamine [mcg/kg/min]/100 + metaraminol [mcg/kg/min]/8 + 2.5*vasopressin[1] [IU/min] + 10*angiotensin II [mcg/kg/min]

   [1]Argipressin is equivalent to vasopressin.

   Patients who discontinued the study during the first 24 hours after the start of the treatment period are assumed to be non-responders.

   Patients who ended the vasopressor treatment during the first 24 hours after the start of the treatment period are considered as responders.

The comparison of treatment groups will be conducted using a weighted Cochran-Mantel-Haenszel framework with two stratification factors (according to SAS terminology): presence of the atrial fibrillation and site.

Hypothesis that Group L is superior to Group C in proportion of patients who reached the primary endpoint will be demonstrated if lower limit of two-sided 95% Newcombe confidence interval of difference pL - pC is above zero, where pL and pC are percentages of patients who reached the primary endpoint in Group L and Group C, respectively. P-value based on the Cochran-Mantel-Haenszel Statistics for testing of statistical significance of association between treatment group and outcome after adjustment for stratification factors will be presented together with the confidence intervals.

The analysis will be primarily performed using FAS. To conclude, the hypotheses need to be demonstrated using FAS and supported by analysis using PPS. Which means that the hypotheses will be either demonstrated using both FAS and PPS or, if not demonstrated using PPS, it will be due to lower sample size in PPS than in FAS and not due to change of effect size.

Supportive analyses for exploratory purposes:
The following individual criteria of the primary endpoint will be analysed separately in the same way as the primary response:

1) Heart rate target achieved

   For the patients who discontinued the study during the first 24 hours, the response will be evaluated from the values measured before their discontinuation.

2) Heart rate target achieved and maintained (heart rate response)

   Patients who discontinued the study during the first 24 hours after the start of the treatment period are assumed to be non-responders.

3) Vasopressor response

   Patients who discontinued the study during the first 24 hours after the start of the treatment period are assumed to be non-responders.

Subgroup analysis by strata or analysis with adjustment for other covariates using log-binomial regression model can be performed for exploratory purposes.

7.3.3 Secondary analyses - Analysis of pharmacodynamic data and dosing

Analysis of secondary endpoints will be performed using FAS and PPS.

For secondary analyses, no multiplicity adjustment is planned; therefore, higher rate of type-I error must be considered when interpretating the results of secondary analyses. The analysis of secondary endpoints can provide supportive evidence related to the primary objective, but no confirmatory conclusion based on the secondary analyses can be done. Confidence intervals and statistical tests in the secondary analysis will be of exploratory nature.

Continuous and binary variables measured at more time-points will be analysed as longitudinal data by linear, logistic, or log-binomial regression models with repeated measures. For continuous data, it is a Mixed Model with Repeated Measures (MMRM) implemented in PROC MIXED in SAS. The calculation of (ordinal) logistic regression will be performed using method Generalized Estimating Equations (GEE) implemented in PROC GENMOD in SAS. Comparison of treatment groups in binary endpoints using relative risk reduction calculated by log-binomial regression model is preferred.

The time-to-event data will be analysed using Kaplan-Meier curve and log-rank test or Wilcoxon test (the choice will be based on the check of assumptions); the Cox proportional regression hazard model will also be performed if assumptions are fulfilled.
Covariates used in the models will be (but not limited to) **treatment**, **visit**, **stratification group** (real value), interaction **treatment*visit**, **site/country**, and interaction **site/country*treatment**. The first choice is to use the effect of site and its interaction with treatment; when it is not possible because of low number of patients in some of the sites, the country will be used; if the model with country is also not suitable (especially for subgroups' analyses), this effect will not be used. For continuous variables, the **baseline value** of the outcome variable will be covariate as well. Distribution of data and feasibility check of planned analyses will be performed before finalization of SAP and alternative statistical methods will be defined if assumptions of used of the planned methods are not met (e.g. ln-transformation of data, non-parametric method, or other alternative way).

Vasopressor requirements over the study period

The vasopressors' usage is recorded mostly in the Solicited Concomitant Medication dataset. The vasopressors are identified by the ATC CODE 4 equal to **C01CA** (ADRENERGIC AND DOPAMINERGIC AGENTS) or **H01BA** (VASOPRESSIN AND ANALOGUES).

Change in vasopressor requirements over the study period will be analysed through the norepinephrine equivalent score (Goradia [4], see Section 7.3.2). The actual values of the score at 0h, 2h, 6h, 12h, 18h and 24h will be summarized by treatment arms. Average score for the following days until Day 28 will be also

summarised (only the total administered amount of the drugs is recorded after the end of titration phase). The change from the 0h score will also be evaluated.

The values of the score after the end of vasopressors treatment are assumed to be 0. The bolus application of vasopressors is not included in the score evaluation.

The difference between the treatment arms in the score will be compared by longitudinal analyses; only timepoints when at least 25% patients in the study are treated with vasopressors will be included in the analysis. To improve normality, a transformation (i.e. square-root transformation) of the response and the baseline score value could be used.

The number of patients with at least one bolus application of a vasopressors in the Titration, Maintenance I and Maintenance II periods will be presented by treatment arms.

Duration of the vasopressors use will be calculated as difference between the End of Vasopressors Treatment Visit and the beginning of the treatment period. The treatment groups will be compared by linear model.

The total amount of administered vasopressors and the average dose per kg and min (IU per min for vasopressin) in the titration phase, in the Maintenance Phase I, Maintenance Phase II and during the whole study will be summarized separately for each drug. No treatment group comparison will be done.

Daily inotropic requirements

The inotropic agents are the following: Dobutamine and all the drugs with ATC4 code C01CE or C01CX.

The duration of the use of inotropic agents (difference between the last administration of an agent and the beginning of treatment period) and the total and daily dose of each agent will be analysed in the same way as the use of vasopressors.

28 day mortality and ICU mortality

The mortality will be analysed using the same method as the primary endpoint. For the ICU mortality, the patients not discharged from ICU on Day 28 are assumed to be survivors.

Moreover, the survival time (difference between time of death and the treatment start) will be analysed as time-to event data.

Duration of ICU stay and duration of hospital stay in (survivors/non-survivors)

For the patients who did not die during the study, the duration of ICU stay and hospitalization (difference between end of ICU hospitalization/ hospitalization and the time of treatment start) will be analysed as time-to-event data.

SOFA score

SOFA score ranges from 0 (normal) to 24 (the worst degree of dysfunction/failure) and is planned to be analysed as continuous variable. It was evaluated for the visits before the end of vasopressors treatment only. The values and changes from baseline will be summarized by treatment arms for the patients still treated by vasopressors and compared by linear model for each visit separately. If there is no major violation of normal distribution, no transformation is needed.

7.3.4 Secondary exploratory analyses

The heart rate and blood pressure (MAP, SAP, and DAP) will be analysed during the titration phase (every hour) and maintenance phases (every 24h), before the end of vasopressors treatment only. The values, changes from baseline and relative changes from baseline will be summarized by treatment arms for the patients still treated by vasopressors and compared by linear model for each visit separately. If there is no major violation of normal distribution, no transformation is needed.

7.3.5 Multicentre data analysis

This study is conducted in 7 countries and 20 sites. For evaluation of effect of country or effect of site, the country or site, and interaction of country/site with treatment was added as covariate into the analyses. In case of an effect of the sites on the treatment, the site or country will be added in all analyses, as is described in Sections 7.3.2 and 7.3.3

7.4 ANALYSES OF SAFETY

The safety endpoints are the following:

- Incidence of Adverse Events (AE)
- Incidence of Serious Adverse Events (SAE)
- Incidence of new onset arrhythmia (HLGT_Term = Cardiac arrhythmias)
- Occurrence of bradycardic episodes (Preferred term = Bradycardia, only listed)

7.4.1 Adverse events

Detailed definition of AE and its classification is presented in the Study Protocol.

Adverse events will be coded using MedDRA dictionary version 25.0 (Mar 2022).

Reconciliation of serious adverse events (i.e., a comparison of the number of SAEs in the clinical database and the number of SAEs reported to sponsor) will be done before DB lock. Coding should be done and approved by the sponsor before DB lock, as well.

The treatment emergent adverse event (TEAE) is each AE which started at the time of the first study drug (start of the titration phase) or later.

Absolute and relative frequencies of patients with treatment emergent adverse events, count and incidence rate of events overall and by MedDRA primary System Organ Class and Preferred Term will be calculated for each treatment arm and overall.

The frequency tables of AEs will present the following types of events separately: treatment emergent adverse events, serious adverse events (SAEs), events leading to death, events leading to study discontinuation and events leading to dose reduction. Further, frequency tables by relationship to study drug (related or not related) and by intensity (Grade 1 to Grade 5) will be displayed.

No statistical tests will be performed.

7.4.2 Other Safety Data

Haematology, coagulation, clinical chemistry, and heart enzyme results will be measured in the clinic's local laboratory. The following parameters will be collected:

- Haematology: Haemoglobin (Hb), Haematocrit (Hct), Red blood cell count (RBC), White blood cell count (WBC), Platelets (PLT).
- Clinical chemistry: Alanine amino-transferase (ALT), Aspartate amino-transferase (AST), Gamma-glutamyl transferase (GGT), Lactate dehydrogenase (LDH), Total bilirubin (BILT), Direct bilirubin (BILD), Amylase (AMY), Lipase (LIP), Creatinine (CRE), Urea-N (BUN), Creatinine-kinase (CK), Myoglobin (MY), N-terminal pro-B-type natriuretic peptide (NT-proBNP) or B-type natriuretic peptide (BNP), C-reactive protein (CRP), Albumin, Total protein, Glucose, Sodium, Potassium, Calcium, Chloride, Magnesium
- Heart enzymes: Creatinine kinase-isoenzyme MB (CK-MB), cardiac Troponin T (cTnT) or cardiac Troponin I (cTnI) or high-sensitive cardiac troponin T (hs-cTnT) or high-sensitive cardiac troponin I (hs-cTnI)
- Coagulation: Prothrombin time (PT, [Quick value]), activated partial thromboplastin time (aPTT), Fibrinogen.

All laboratory data will be converted to standard units. The standard units and conversion to the units was confirmed by Sponsor and can be find in file *LB_Units conversion 14APR2022.xlsx*.

Blood gas parameters (FiO2, PaO2, SaO2, SvO2 or ScvO2, PaCO2, arterial pH, base excess, bicarbonate (HCO3), arterial lactate level) and SOFA Score (PaO2/FiO2, Glasgow coma scale (actual status), MAP or "administration of vasopressors required", Bilirubin, Platelets, Creatinine) will be also analysed.

Summary tables presenting descriptive statistics and the number of patients with values below, within and above the reference range will be presented for each laboratory parameter, SOFA score and physical examination at each time-point of assessments.

7.5 INTERIM ANALYSES

No interim analysis is planned.

7.6 DETERMINATION OF SAMPLE SIZE

Assuming that the primary endpoint reaches 60% of patients in Group L vs. 40% of patients in Group C a total number of 194 patients (97 patients in each treatment group) will provide 80% power to demonstrate statistically significant difference between treatment groups using Chi-square test at level of significance alpha=5%.

The sample size was calculated using Statistical Analysis System (SAS®) software, version 9.4 (SAS Institute, Cary, NC, USA). SAS program for the sample size calculation is the following:

```
proc power;
  twosamplefreq test=pchi
  alpha=0.05
  proportions=(0.6 0.4)
  ntotal= .
  power = 0.80;
run;
```

The primary endpoint is measured at 24 hours after treatment start. Patients who died during first 24 hours without reaching of the primary endpoint will be included in the analysis (with the outcome that the primary endpoint was not reached); therefore, no drop-out from the primary analysis is assumed. Taking the application of block randomization stratified in two stratification groups into account, the total number of patients to be randomized is set to 200 (100 patients in each treatment group).

Because of stratification of the randomization with respect to the presence / not presence of atrial fibrillation without knowing the proportion of patients with atrial fibrillation at the beginning of the study, there were 101 patients randomized into Group C and 99 patients randomized into Group L. Because the sample size to get the required power of the test for the primary response was 97 patients in each treatment group, the power will not be compromised.

8 LIST OF TABLES, FIGURES AND LISTINGS

The table hereunder presents preliminary list of content of tables, figures and listings which will be integrated in the study report. The structure and numbering are proposed according to the ICH guidelines - E3: Structure and Content of Clinical Study Reports.

8.1 Section 14 of CSR (TABLES AND FIGURES REFERRED TO BUT NOT INCLUDED IN THE TEXT)

14.1 Disposition and characteristics of the patients

14.1.1 Disposition of study patients

Table 14.1.1.1 Disposition of patients by treatment arms and reasons for premature discontinuation
Table 14.1.1.2.1 Disposition of patients by visits (FAS)
Table 14.1.1.2.2 Disposition of patients by visits (PPS)
Table 14.1.1.3.1 Duration of the stay in the study by treatment arms (FAS)
Table 14.1.1.3.2 Duration of the stay in the study by treatment arms (PPS)
Table 14.1.1.4.1 Frequencies of patients per country and site (FAS)
Table 14.1.1.4.2 Frequencies of patients per country and site (PPS)

14.1.2 Protocol deviations

Table 14.1.2.1 Major study protocol deviations

14.1.3 Baseline characteristics of study patients

Table 14.1.3.1.1 Baseline characteristics by treatment arms (FAS)
Table 14.1.3.1.2 Baseline characteristics by treatment arms (PPS)
Table 14.1.3.2.1 Summary of medical history by treatment arms (FAS)
Table 14.1.3.2.2 Medical history by treatment arms (FAS)
Table 14.1.3.3.1 Previous medication by treatment arms (FAS)
Table 14.1.3.4.1 Concomitant medication by treatment arms (FAS)
Table 14.1.3.5.1 Previous treatment by treatment arms (FAS)
Table 14.1.3.6.1 Concomitant treatment by treatment arms (FAS)

14.2 Efficacy data

All the tables in Sections 14.2.1 and 14.2 are prepared for the FAS and for the PPS sets; the x in the tables numbering means x=1 for FAS, x=2 for PPS

When comparison by models is used, more tables could be produced for an endpoint to get all the required information (this is especially valid for the primary endpoints).

14.2.1 Exposure to study drug

Table 14.2.1.1.x Duration of the study drug (Landiolol) treatment (x=1 FAS / x=2 PPS)
Table 14.2.1.2.x Dosage of the study drug (Landiolol) during the study (x=1 FAS / x=2 PPS)
Figure 14.2.1.1.x Boxplot of the dosage of the study drug (Landiolol) (x=1 FAS / x=2 PPS)

14.2.2 Primary efficacy

Table 14.2.2.1.x Analyses of percentage of the patients with the primary response (x=1 FAS / x=2 PPS)
Table 14.2.2.2.x Analyses of percentage of the patients with the heart rate target achieved (x=1 FAS / x=2 PPS)
Table 14.2.2.3.x Analyses of percentage of the patients with the heart rate response (heart rate target reached and maintained) (x=1 FAS / x=2 PPS)
Table 14.2.2.4.x Analyses of percentage of the patients with the vasopressor response (x=1 FAS / x=2 PPS)

14.2.3 Secondary efficacy

14.2.3.1 Vasopressor requirements over the study period

Table 14.2.3.1.1.x Norepinephrine equivalent score during the study by treatment arms (x=1 FAS / x=2 PPS)
Figure 14.2.3.1.1.x Norepinephrine equivalent score during the study (x=1 FAS / x=2 PPS)

Table 14.2.3.1.1.y Results of the model for norepinephrine equivalent score during the study (y=3 FAS / y=4 PPS)

Table 14.2.3.1.2 Number of patients with bolus administration of vasopressors in the study periods (FAS, PPS)

Table 14.2.3.1.3.x Duration of vasopressors administration in the study (x=1 FAS / x=2 PPS)

Table 14.2.3.1.4.x Total and average dose of vasopressors in the study periods (x=1 FAS / x=2 PPS)

14.2.3.2 Inotropic requirements

Table 14.2.3.2.1.x Duration of inotropic agents administration in the study (x=1 FAS / x=2 PPS)

Table 14.2.3.2.1.x Total and average dose of inotropic agents in the treatment periods (x=1 FAS / x=2 PPS)

14.2.3.3 28 day mortality and ICU mortality

Table 14.2.3.3.1.x Summary of 28-day mortality by treatment arms (x=1 FAS / x=2 PPS)

Table 14.2.3.3.2.x Time of survival by treatment arms (x=1 FAS / x=2 PPS)

Figure 14.2.3.3.2.x Kaplan - Meier curve for the time to death (x=1 FAS / x=2 PPS)

Table 14.2.3.3.3.x Summary of ICU 28-day mortality by treatment arms (x=1 FAS / x=2 PPS)

14.2.3.4 Duration of ICU stay and duration of hospital stay

Table 14.2.3.4.1.x Duration of ICU stay for survivors by treatment arms (x=1 FAS / x=2 PPS)

Figure 14.2.3.4.1.x Kaplan - Meier curve for the duration of ICU stay for patients alive on Day 28 (x=1 FAS / x=2 PPS)

Table 14.2.3.4.2.x Duration of hospital stay for survivors by treatment arms (x=1 FAS / x=2 PPS)

Table 14.2.3.4.2.x Duration of hospital stay for patients alive on Day 28 by treatment arms (x=1 FAS / x=2 PPS)

14.2.3.5 SOFA score

Table 14.2.3.5.1.x Descriptive statistics of SOFA score by visit (x=1 FAS / x=2 PPS)

14.2.3.6 Heart Rate and Blood Pressure

Table 14.2.3.6.1.x Descriptive statistics of Heart Rate by visit (x=1 FAS / x=2 PPS)

Table 14.2.3.6.2.x Descriptive statistics of Mean Blood Pressure by visit (x=1 FAS / x=2 PPS)

Table 14.2.3.6.3.x Descriptive statistics of Systolic Blood Pressure by visit (x=1 FAS / x=2 PPS)

Table 14.2.3.6.4.x Descriptive statistics of Diastolic Blood Pressure by visit (x=1 FAS / x=2 PPS)

Figure 14.2.3.6.1.1 Heart rate by treatment groups in the titration phase (Safety)

Figure 14.2.3.6.1.2 Heart rate by treatment groups during the study (Safety)

Figure 14.2.3.6.2.1 Systolic, diastolic, and mean arterial pressure by treatment groups in the titration phase (Safety)

Figure 14.2.3.6.2.2 Systolic, diastolic, and mean arterial pressure by treatment groups during the study (Safety)

14.3 Safety data

14.3.1 Adverse events

Table 14.3.1.1 Summary of all adverse events (Safety)

Table 14.3.1.2 All treatment-emergent adverse events by MedDRA preferred term within primary SOC (Safety)

Table 14.3.1.3 All treatment-emergent serious adverse events by MedDRA preferred term within primary (Safety)

Table 14.3.1.4 All treatment-emergent adverse events by intensity and by MedDRA preferred term within primary SOC (Safety)

Table 14.3.1.5 All treatment-emergent serious adverse events by intensity and by MedDRA preferred term within primary SOC (Safety)

Table 14.3.1.6 All treatment-emergent adverse events leading to study discontinuation by MedDRA preferred term within primary SOC (Safety)

Table 14.3.1.7 All treatment-emergent adverse events leading to dose reduction by MedDRA preferred term within primary SOC (Safety)

Table 14.3.1.8 All treatment-emergent adverse events leading to dose interruption by MedDRA preferred term within primary SOC (Safety)

Table 14.3.1.9 All treatment-emergent adverse events leading to death by MedDRA preferred term within primary SOC (Safety)

Table 14.3.1.10 Listing of all treatment-emergent bradycardic episodes (Safety)

14.3.2 Other Safety

Table 14.3.2.1 Haemoglobin [g/dL] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.2.2 Haematocrit [%] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.2.3 Platelets [10^9/L] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.2.4 Erythrocytes [10^{12}/L] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.2.5 Leukocytes [10^9/L] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.1 Aspartate amino-transferase (AST) [U/L] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.2 Alanine amino-transferase (ALT) [U/L] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.3 Gamma-glutamyl-transpeptidase (GGT) [U/L] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.4 Lactate dehydrogenase (LDH) [U/L] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.5 Total bilirubin (BILT) [mg/dL] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.6 Direct bilirubin (BILD) [mg/dL] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.7 Amylase (AMY) [U/L] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.8 Lipase (LIP) [U/L] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.9 Creatinine (CRE) [mg/dL] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.10 Urea-N (BUN) [mg/dL] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.11 Creatine-kinase (CK) [U/L] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.12 Myoglobin (MY) [ng/mL] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.13 N-terminal pro-B-type natriuretic peptide (NT-proBNP) [pg/mL] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.14 B-type natriuretic peptide (BNP) [pg/mL] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.15 C-reactive protein (CRP) [mg/L] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.16 Albumin [g/L] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.17 Total protein [g/L] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.18 Sodium (Na+) [mmol/L] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.19 Potassium (K+) [mmol/L] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.20 Calcium (Ca2+) [mmol/L] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.21 Chloride (Cl-) [mmol/L] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.22 Magnesium (Mg2+) [mmol/L] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.3.23 Glucose [mg/dL] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.4.1.1 Prothrombin time (PT, [Quick value]) [%] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.4.1.2 Prothrombin time (PT, [Quick value]) [sec] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.4.1.3 Prothrombin time (PT, [Quick value]) [ratio] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.4.2.1 Activated partial thromboplastin time (aPTT) [sec] (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.4.2.2 Activated partial thromboplastin time (aPTT) [ratio] (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.4.3 Fibrinogen [mg/dL] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.5.1.1 Creatine Kinase-isoenzyme MB (CK-MB) - activity [U/L] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.5.1.2 Creatine Kinase-isoenzyme MB (CK-MB) - mass [ug/mL] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.5.2.1 Cardiac Troponin T (cTnT) [ng/L] (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.5.2.2 High-sensitive Cardiac Troponin T (HS cTnT) [ng/L] (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.5.3.1 Cardiac Troponin I (cTnI) [ng/L] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.5.3.2 High-sensitive Cardiac Troponin I (HS cTnI) [ng/L] by visit (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.6.1 FiO2 [%] (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.6.2 PaO2 [mmHg] (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.6.3 SaO2 [%] (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.6.4 SvO2 [%] (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.6.5 ScvO2 [%] (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.6.6 PaCO2 [mmHg] (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.6.7 Bicarbonate (HCO3) [mmol/L] (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.6.8 Arterial lactate level [mmol/L] (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.6.9 Arterial pH (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.6.10 Base excess [mmol/L] (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)Table 14.3.7.1 Daily fluid intake [mL] by visit (descriptive statistics of values) (Safety)

Table 14.3.7.2 Daily fluid output [mL] by visit (descriptive statistics of values) (Safety)

Table 14.3.7.3 Daily fluid balance [mL] by visit (descriptive statistics of values) (Safety)

Table 14.3.8.1 SOFA score: Respiration (PaO2/FiO2 or SaO2/FiO2 (mmHg)) by visit (Safety)

Table 14.3.8.2 SOFA score: Coagulation (Platelets (10_9/L)) by visit (Safety)

Table 14.3.8.3 SOFA score: Liver Bilirubin (mg/dL) by visit (Safety)

Table 14.3.8.4 SOFA score: Cardiovascular Hypotension by visit (Safety)

Table 14.3.8.5 SOFA score: Glasgow Coma Score by visit (Safety)

Table 14.3.8.6 SOFA score: Renal Creatinine (mg/dL) or urine output (mL/d) by visit (Safety)

Table 14.3.8.7 SOFA score (descriptive statistics) by visit

Table 14.3.9.1 Physical examination (frequencies of normal and abnormal findings by organ system) (Safety)

Table 14.3.9.2 Physical examination (descriptive statistics of weight, height, and BMI) (Safety)

Table 14.3.9.3 Physical examination - body temperature [°C] (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.10.1 Basic haemodynamic parameters - Heart rate [bpm] (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.10.2 Basic haemodynamic parameters - mean arterial pressure [mmHg] (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.10.3 Basic haemodynamic parameters - systolic arterial pressure [mmHg] (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

Table 14.3.10.4 Basic haemodynamic parameters - diastolic arterial pressure [mmHg] (descriptive statistics of values and frequencies of normal and abnormal values) (Safety)

8.2 Appendix 16.2 of CSR (PATIENT DATA LISTINGS AND PROFILES)

All subjects included in clinical database will be listed (if not specified otherwise). Main areas are the following:

16.2.1 Discontinued subjects

16.2.2 Protocol Deviations

16.2.3 Subjects excluded from efficacy analysis

16.2.4 Demographic data

16.2.5 Compliance and drug concentration data

16.2.6 Individual efficacy response data

16.2.7 Adverse events listings

16.2.8 Listing of individual laboratory measurements

16.2.9 Listing of Daily fluid balance

16.2.10 Listing of SOFA score

16.2.11 Listing of physical examination

16.2.12 Listing of basic haemodynamic parameters

REFERENCES

[1] ICH guidelines - E3: Structure and Content of Clinical Study Reports, Adopted in EU by CPMP, December 95, issued as CPMP/ICH/137/95

[2] ICH guidelines - E9: Statistical Principles for Clinical Trials, Adopted in EU by CPMP, March 1998, issued as CPMP/ICH/363/96

[3] SAS 9.4; © 2014 by SAS Institute Inc., Cary, NC, USA; OnLine Doc.

[4] Goradia S, Sardaneh AA, Narayan SW, Penm J, Patanwala AE: Vasopressor dose equivalence: A scoping review and suggested formula. Journal of Critical Care 61/2021 p. 233-240, https://doi.org/10.1016/j.jcrc.2020.11.002.

DOCUMENT HISTORY

Version	Date	Description of change	Performed by
Draft 0.1	22-MAR-2021	First version of the document created.	Marie Šimečková
Draft 0.2	28-JAN-2022	Document update based on the communication with sponsor.	Marie Šimečková
Draft 0.3	25-MAR-2022	Document update based on the communication with sponsor.	Marie Šimečková
Draft 0.4	15-APR-2022	Document update based on the communication with sponsor.	Marie Šimečková
Draft 0.5	21-APR-2022	Lactate, Arterial pH at baseline clarified.	Marie Šimečková
Final 1.0	27-APR-2022	Adding HR and blood pressure analyses. Finalization.	Marie Šimečková