FERRING
PHARMACEUTICALS

Protocol

Title of trial: A Double-blind, Randomised, Placebo-controlled, Phase 2b/3 Adaptive Clinical Trial Investigating the Efficacy and Safety of Selepressin as Treatment for Patients with Vasopressor-dependent Septic Shock
NCT number: NCT02508649
Sponsor trial code: 000133
Date: 08 Jul 2016

CLINICAL TRIAL PROTOCOL

A Double-blind, Randomised, Placebo-controlled, Phase 2b/3 Adaptive Clinical Trial Investigating the Efficacy and Safety of Selepressin as Treatment for Patients with Vasopressor-dependent Septic Shock

Trial Code: 000133

SEPSIS-ACT
Selepressin Evaluation Programme for Sepsis-Induced Shock–Adaptive Clinical Trial

Note: This is a consolidated protocol including all changes stated in:

- ***Protocol Amendment 01 (implemented prior to trial start)***
- ***Protocol Amendment 02***

EudraCT Number:	2014-003973-41
IND Number:	77246
Investigational Medicinal Products:	Selepressin; concentrate for solution for infusion Placebo; sterile 0.9% sodium chloride solution
Indication:	Vasopressor-dependent septic shock
Phase:	2b/3
Name and Address of Sponsor:	Ferring Pharmaceuticals A/S Clinical Research and Development Kay Fiskers Plads 11 2300 Copenhagen S, Denmark Telephone number: +45 88 33 88 34
GCP Statement:	This trial will be performed in compliance with GCP

SYNOPSIS

TITLE OF TRIAL

A Double-blind, Randomised, Placebo-controlled, Phase 2b/3 Adaptive Clinical Trial Investigating the Efficacy and Safety of Selepressin as Treatment for Patients with Vasopressor-dependent Septic Shock

SEPSIS-ACT / Selepressin Evaluation Programme for Sepsis-Induced Shock - Adaptive Clinical Trial

SIGNATORY INVESTIGATORS

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[redacted] Medical-surgical Intensive Care Unit, Saint Luc University Hospital at the Université Catholique de Louvain, Brussels, Belgium.

TRIAL SITES

The trial will be conducted predominately across Europe and North America at approximately 60-100 trial sites in total.

PLANNED TRIAL PERIOD	CLINICAL PHASE
First visit for the first patient is planned for Q3 2015. Last visit for the last patient is expected in Q4 2018.	2b/3

OBJECTIVES

Primary objective

- To demonstrate superiority of selepressin plus standard care versus placebo plus standard care in the number of vasopressor- and mechanical ventilator-free days (with penalty for mortality) in patients with vasopressor-dependent septic shock

Secondary objectives

- To determine the efficacy of selepressin on:
  - Organ dysfunction
  - Morbidity and mortality
  - Fluid balance
  - Health-related quality of life
- To determine the safety profile of selepressin
- To determine the pharmacokinetics of selepressin
- To determine the health economics of selepressin
- To further evaluate a range of biomarkers in relation to the mode of action of selepressin

ENDPOINTS

Primary endpoint

- Vasopressor- and mechanical ventilator-free days (P&VFDs) up to Day 30

  This composite endpoint is defined as the number of days (reported to one decimal place [0.0 to 30.0 days]) from start of treatment with the investigational medicinal product (IMP) [selepressin or placebo] to 30.0 days thereafter during which the patient is: 1) alive; 2) free of treatment with intravenous vasopressors; and 3) free of any invasive mechanical ventilation (see definition below).

  Any patient that dies within this 30-day period is assigned zero P&VFDs, even if there is a period during which the patient is free of both vasopressor treatment and mechanical ventilation. If vasopressors need to be restarted or mechanical ventilation needs to be initiated or restarted, and the use of either is greater than 60 minutes within a 24-hour period, then the clock is reset and the patient is not considered free of vasopressors and/or mechanical ventilation until after those therapies are again finally discontinued. Vasopressor use or mechanical ventilation during - and up to three hours after - surgery / procedure (including bedside) is exempt from this rule (i.e. does not reset the calculation of P&VFDs). The intent is for the endpoint to reflect the speed of recovery from septic shock and respiratory failure, with appropriate penalties for recurrent shock, new or recurrent respiratory failure, and death.

  Vasopressor use is defined as any intravenous dose of norepinephrine/noradrenaline, phenylephrine, dopamine, epinephrine/adrenaline, vasopressin, terlipressin, and IMP (i.e. selepressin and placebo).

  Mechanical ventilation is defined as use of endotracheal or tracheostomy tube assisted ventilation (>5 cm H_2O continuous positive airway pressure and >5 cm H_2O of pressure support from the ventilator in tracheostomy patients). End of mechanical ventilation is defined as: 1) extubation of intubated patients or 2) ≤5 cm H_2O continuous positive airway pressure and ≤5 cm H_2O of pressure support from the ventilator in tracheostomy patients. If non-invasive ventilation by mask or bag (>5 cm H_2O of pressure support) is deployed to avoid (re)intubation, it also counts as mechanical ventilation. However, all other uses of non-invasive ventilation such as chronic night-time use of positive airway pressure for chronic obstructive pulmonary disease (COPD) or sleep apnea does not count as mechanical ventilation (regardless of pressure).

Key secondary endpoints

- All-cause mortality (defined as the fraction of patients that have died, regardless of cause) at Day 90
- Renal replacement therapy (RRT)-free days up to Day 30 (excluding patients on RRT for chronic renal failure at time of randomisation)
- Intensive care unit (ICU)-free days up to Day 30

Secondary efficacy endpoints

Organ dysfunction

- Vasopressor-free days up to Day 30
- Mechanical ventilator-free days up to Day 30
- Duration of septic shock (i.e. vasopressor use) up to Day 30
- Duration of mechanical ventilation up to Day 30
- Incidence of RRT up to Day 30 (counting patients who die as on RRT and excluding patients on RRT for chronic renal failure at time of randomisation)
- Duration of RRT up to Day 90 (excluding patients on RRT for chronic renal failure at time of randomisation)
- Daily overall and individual organ (cardiovascular, respiratory, renal, hepatic, coagulation) scores using a modified version of the Sequential Organ Failure Assessment (SOFA) until ICU discharge
- Incidence of new organ dysfunction and new organ failure (based on the SOFA score) up to Days 7 and 30

Morbidity and mortality

- ICU length of stay up to Day 30
- All-cause mortality (defined as the fraction of patients that have died, regardless of cause) at Days 30 and 180

Fluid balance

- Daily and cumulative fluid balance until ICU discharge (for a maximum of 7 days)
- Daily and cumulative urine output until ICU discharge (for a maximum of 7 days)

Health-related quality of life

- Change in utility, based on the EuroQol group's 5-dimension 5-level (EQ-5D-5L) questionnaire, up to Day 180

Safety endpoints

- Incidence of adverse events (type, frequency, and intensity) with specific emphasis on:
  - Ischaemic events (e.g. myocardial, skin, cerebral, mesenteric, and limb ischaemia)
- Changes in vital signs and safety laboratory variables, including:
  - Number of clinically significant results assessed as unanticipated in the setting of septic shock
- Episodes of hypotension (mean arterial pressure <60 mmHg for longer than one hour)

Additional endpoints

- Hospital-free days up to Day 90
- Hospital length of stay up to Day 90

- Patient residence at Day 30, Day 60, Day 90, and Day 180
- Health economic evaluation - to be reported separately according to a pre-specified health economic analytical plan
- Mean arterial pressure (MAP), until ICU discharge (for a maximum of 7 days)
- Norepinephrine/noradrenaline and other vasopressor doses
- Pharmacokinetic response (in a subset of approximately 200 patients) - to be reported separately according to a pre-specified pharmacokinetic analysis plan
- Creatinine clearance
- Ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2 ratio) (in a subset of 100-350 patients)
- Extravascular lung water and pulmonary permeability index (in a subset of 100-350 patients)
- Cardiac output (in a subset of 100-350 patients)
- Cytokines (in a subset of 100-350 patients)
- Angiopoietin-1 and -2 (in a subset of 100-350 patients)

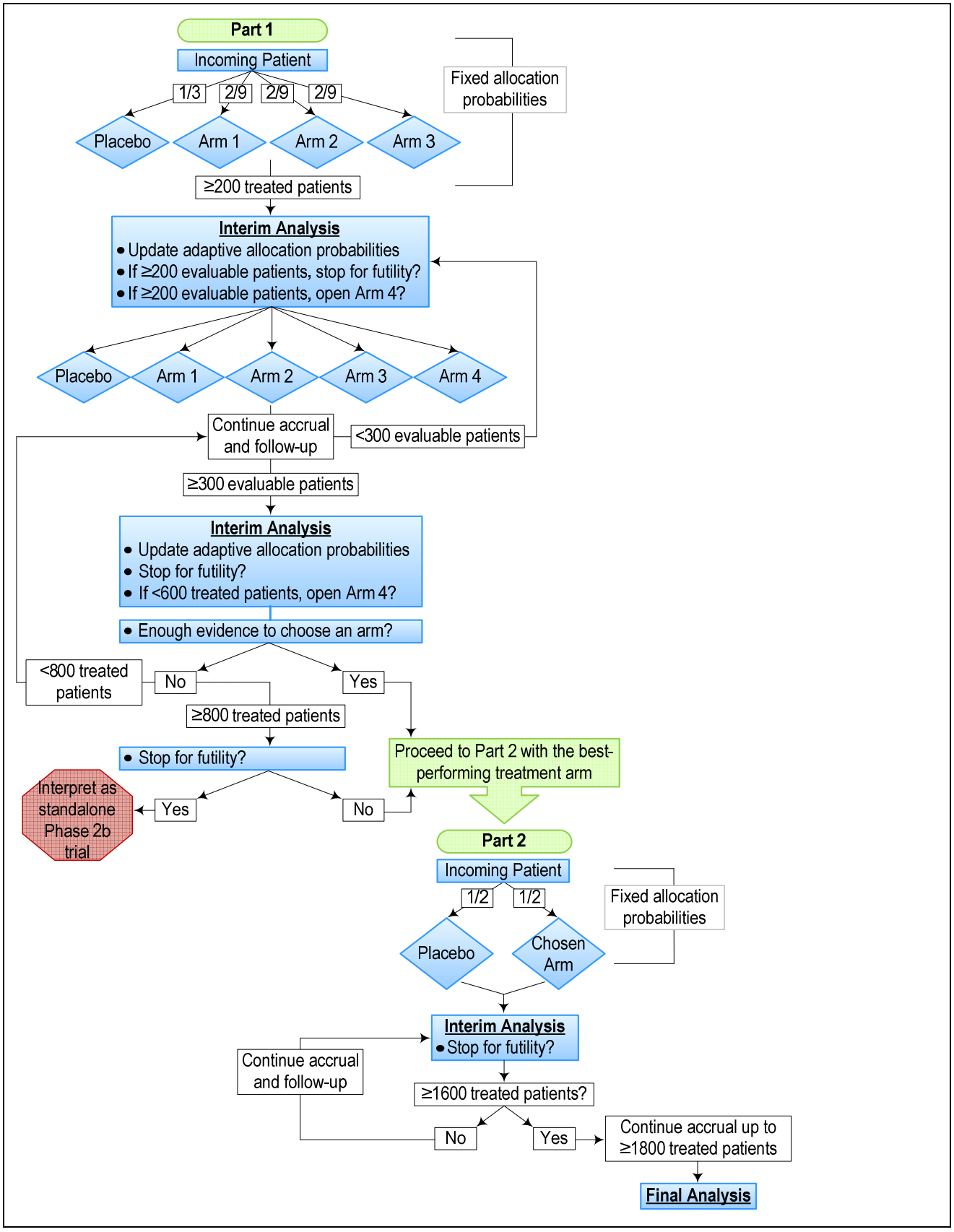
METHODOLOGY

This is a double-blind, randomised, placebo-controlled, two-part adaptive clinical trial. The trial is designed to investigate the efficacy and safety of multiple dosing regimens of selepressin and to confirm the efficacy and safety of one dosing regimen in treatment of adult patients with septic shock requiring vasopressor.

Up to four dosing regimens of selepressin will be investigated:

Treatment Arm	Starting Dose (ng/kg/min)	Maximum Dose (ng/kg/min)	Range (ng/kg/min)
Arm 1	1.7	2.5	0-2.5
Arm 2	2.5	3.75	0-3.75
Arm 3	3.5	5.25	0-5.25
Arm 4	5.0	7.5	0-7.5

The overall trial design includes two parts (Part 1 – Phase 2b and Part 2 – Phase 3) as illustrated on the next page.


Part 1
Incoming Patient
1/3
2/9
2/9
2/9
Placebo
Arm 1
Arm 2
Arm 3
Fixed allocation probabilities
≥200 treated patients
Interim Analysis
• Update adaptive allocation probabilities
• If ≥200 evaluable patients, stop for futility?
• If ≥200 evaluable patients, open Arm 4?
Placebo
Arm 1
Arm 2
Arm 3
Arm 4
Continue accrual and follow-up
<300 evaluable patients
≥300 evaluable patients
Interim Analysis
• Update adaptive allocation probabilities
• Stop for futility?
• If <600 treated patients, open Arm 4?
• Enough evidence to choose an arm?
<800 treated patients
No
Yes
≥800 treated patients
• Stop for futility?
Interpret as standalone Phase 2b trial
Yes
No
Proceed to Part 2 with the best-performing treatment arm
Part 2
Incoming Patient
1/2
1/2
Placebo
Chosen Arm
Fixed allocation probabilities
Interim Analysis
• Stop for futility?
Continue accrual and follow-up
≥1600 treated patients?
No
Yes
Continue accrual up to ≥1800 treated patients
Final Analysis

Part 1 is a dose-finding stage with response-adaptive randomisation to preferentially allocate patients to the dosing regimens that appear to have the maximum benefit with respect to the primary endpoint. Interim analyses will be conducted regularly in Part 1 to optimise the efficiency of selecting the optimal dosing regimen and to allow early termination of the trial for futility. If Part 1 results in a decision to run the second part of the trial, Part 2 will be a 1:1 randomised comparison of the best-performing dosing regimen of selepressin selected in Part 1 versus placebo on top of standard care. All patients will be on norepinephrine/noradrenaline treatment as part of standard of care at the time when the IMP (selepressin or placebo) infusion is initiated.

Before administration, selepressin will be diluted to one of four specific concentrations to allow for blinded administration using similar infusion rates. The infusion of IMP (selepressin or placebo) will start as early as possible and no later than 12 hours after initiation of continuous infusion of vasopressor treatment for septic shock. To ensure start of IMP treatment without delay, informed consent will be obtained, in compliance with local regulations, as early as possible.

During the course of treatment, the IMP infusion rate will be adjusted within pre-defined infusion rates to keep the MAP at the target of 65 mmHg. A different MAP target is acceptable, if it is pre-specified and if it is appropriate, as judged by the investigator, for the clinical management e.g. previous history of hypotension or hypertension (if deemed necessary to maintain adequate organ perfusion). A detailed IMP and vasopressor administration guide will be provided to trial sites. If the administration of IMP in addition to norepinephrine/noradrenaline increases MAP to above the target, norepinephrine/noradrenaline will be weaned first while aiming to keep MAP at the target. Norepinephrine/noradrenaline must be completely weaned prior to weaning of IMP. If norepinephrine/noradrenaline cannot be completely weaned, the infusion rate of IMP is to be increased up to the maximum allowed infusion rate in an attempt to use IMP as the sole vasopressor. If infusion of IMP alone increases the MAP to above the target, the IMP will be weaned step-wise while aiming to keep MAP at the target. If the maximum allowed infusion rate of the IMP is not sufficient to maintain MAP at the target, norepinephrine/noradrenaline will be added to achieve the targeted MAP. If target MAP cannot be maintained despite maximum allowed infusion rate of IMP and ≥1 μg/kg/min norepinephrine/noradrenaline base (or a total catecholamine equivalent of 1 μg/kg/min norepinephrine/noradrenaline base), vasopressin may be added.

The IMP infusion will continue as long as blood pressure support is deemed necessary with a maximum period of 30 days. After complete weaning, IMP infusion may be re-started during this 30-day period for treatment of sepsis-induced hypotension if there is no suspicion of mesenteric or cardiac ischaemia. Patients who still need vasopressor treatment after 30 days will be switched to other vasopressors at the discretion of the investigator.

NUMBER OF PATIENTS

Enough patients will be enrolled in the trial to obtain 1800 evaluable patients in the entire programme (including both parts of the trial).

CRITERIA FOR INCLUSION / EXCLUSION

The intention is to enrol a typical sample of patients presenting with septic shock and commence treatment with the IMP during the initial hours of resuscitation, within 12 hours from onset of vasopressor treatment, targeting those who do not respond rapidly to fluids and whose vasopressor-need persists for at least one hour.

Inclusion criteria

1. 18 years of age or older.
2. Proven or suspected infection.
3. Septic shock defined as hypotension (systolic blood pressure less than 90 mmHg OR MAP less than 65 mmHg) requiring vasopressor treatment (i.e. any dose of norepinephrine / noradrenaline base greater than 5 µg/min) despite adequate fluid resuscitation (at least one litre for hypotension).
4. Informed consent obtained in accordance with local regulations.

Exclusion criteria

1. Not possible to initiate IMP treatment within 12 hours from onset of vasopressor treatment for septic shock.
2. Primary cause of hypotension not due to sepsis (e.g. major trauma including traumatic brain injury, haemorrhage, burns, or congestive heart failure/cardiogenic shock).
3. Previous severe sepsis with ICU admission within this hospital stay.
4. Known/suspected acute mesenteric ischaemia.
5. Suspicion of concomitant acute coronary syndrome based on clinical symptoms and/or ECG during this episode of septic shock.
6. Chronic mechanical ventilation for any reason OR severe COPD requiring either continuous daily oxygen use during the preceding 30 days or mechanical ventilation (for acute exacerbation of COPD) during the preceding 30 days.
7. Received bone marrow transplant during the preceding 6 months or chemotherapy during the preceding 30 days for lymphoma or leukemia.
8. Known to be pregnant.
9. Decision to limit full care taken before obtaining informed consent.
10. Use of vasopressin in the past 12 hours prior to start of the IMP infusion or use of terlipressin within 7 days prior to start of the IMP infusion.
11. Prior enrolment in the trial.
12. Prior use of an investigational medicinal product within the last month OR planned or concurrent participation in a clinical trial for any investigational drug or investigational device.

Eligibility criteria – post-randomisation / before start of IMP infusion
In addition, the following criteria must be met at start of IMP infusion:

1. Received a minimum of 30 mL/kg fluid in total from the onset of hypotension (or less if evidence of fluid replete/overload).
2. Received a continuous infusion of norepinephrine/noradrenaline base greater than 5 µg/min for at least one hour and is still receiving at least 5 µg/min norepinephrine/noradrenaline base.
3. Less than 12 hours since onset of vasopressor treatment for septic shock.

INVESTIGATIONAL MEDICINAL PRODUCTS

- Selepressin 0.3 mg/mL (10 mM acetate buffer, pH 4). Selepressin is provided as a stock solution which will be diluted with sterile 0.9% sodium chloride solution prior to infusion according to a specific dilution protocol.
- Placebo: sterile 0.9% sodium chloride solution.

DURATION OF TREATMENT

All patients will receive IMP (selepressin or placebo) as an intravenous infusion until recovery from the need of vasopressor treatment or for 30 days, whichever comes first. If the need of vasopressor treatment subsides and recurs due to sepsis-induced hypotension within the 30-day treatment period, IMP should be used when possible if there is no suspicion of mesenteric or cardiac ischaemia.

STATISTICAL METHODS

The trial is powered to demonstrate superiority of selepressin plus standard care versus placebo plus standard care in the number of P&VFDs in patients with vasopressor-dependent septic shock.

Primary analysis
If Part 2 of the trial is run, the primary endpoint, P&VFDs, will be analysed using a van Elteren test. The primary analysis will compare all patients on all selepressin arms from both parts of the trial (pooled together and treated as a single arm) to all patients on the placebo arm from both parts of the trial.

The primary analysis will be a test of superiority using a two-sided 5% significance level test. This test, within the trial, controls the type 1 error at a two-sided 5% level.

The analysis will be based on both the full analysis set (FAS) and the per protocol (PP) analysis set, with the FAS being considered the primary analysis to judge statistical significance and the PP analysis considered as supportive. The FAS comprises all randomised (as planned) patients who have received IMP treatment.

Power
The overall power for obtaining statistical significance based on combined evidence from Part 1 and Part 2 is 91% in situations where all 4 arms have a true underlying 1.5% lower mortality rate

and a 1.5-day higher expected number of P&VFDs for survivors (corresponding to an overall treatment effect of 1.5 P&VFDs) as compared to placebo. If the effect sizes are 2% on mortality and 2 days for P&VFDs in survivors for all 4 arms (corresponding to an overall treatment effect of 2 P&VFDs) then the overall power is 98%. In this latter case the probability of engaging into Part 2 is ~99%.

Secondary analyses
The secondary endpoints are aimed at supporting primary efficacy by further demonstrating treatment effect accompanied by an acceptable safety profile.

Endpoints defined as '-free days' will be defined and analysed in a similar manner as the primary endpoint. Endpoints addressing SOFA score, fluid balance, and health-related quality of life as well as all endpoints measuring duration and split in survivors/non-survivors will be analysed by analysis of covariance (ANCOVA) methods and presented graphically. Mortality, incidence of new organ dysfunction, and new organ failure will be analysed by logistic regression. Mortality will be presented graphically by a Kaplan-Meier plot. All secondary endpoints will be analysed using both the FAS and the PP analysis set.

For the purpose of a possible label inclusion, the Hochberg procedure for adjustment on multiplicity will be implemented to selected secondary endpoints. Only if the primary efficacy analysis leads to a statistically significant result at the (one-sided) 2.5% level, then the Hochberg procedure, which is described below, will be applied to selected secondary analyses. If the primary efficacy analysis does not result in statistical significance at the (one-sided) 2.5% level, then statistical significance (for the purpose of a possible label inclusion only) will not be declared for any of the secondary analyses, regardless of their p-values.

The selected key secondary endpoints aimed at further demonstrating treatment effect are:

- All-cause mortality (defined as the fraction of patients that have died, regardless of cause) at Day 90
- RRT-free days up to Day 30 (excluding patients on RRT for chronic renal failure at time of randomisation)
- ICU-free days up to Day 30

In this application of the Hochberg procedure there are three hypothesis tests of superiority for each of the selected secondary endpoints. The target alpha level is (one-sided) 2.5%. The Hochberg procedure is as follows:

- Order the p-values from the smallest to the largest value, $p(1) < p(2) < p(3)$, with corresponding null hypothesis $H_{(1)}$, $H_{(2)}$, and $H_{(3)}$.
- Start with the highest p-value. If $p(3) < 2.5\%$ (one-sided), then stop and declare all three comparisons significant at the 2.5% (one-sided) level (i.e. reject $H_{(1)}$, $H_{(2)}$, and $H_{(3)}$). Otherwise, accept $H_{(3)}$ for the endpoint related to p(3), and go to p(2) the second highest p-value.
- If $p(2) < 2.5/2 = 1.25\%$ (one-sided), then stop and declare significance for $H_{(1)}$ and $H_{(2)}$.

Otherwise, accept $H_{(2)}$, for the endpoint related to p(2), and go to p(1) the lowest p-value.

- If $p(1) < 2.5/3 = 0.833\%$ (one-sided), then stop and declare significance for $H_{(1)}$. Otherwise, accept $H_{(1)}$, for the endpoint related to p(1).

Regardless of the statistical significance declared according to the Hochberg procedure, all analysis will be included and presented in the statistical report.

The safety profile, including adverse events, vital signs, and safety laboratory variables, will be summarised descriptively. The safety analyses will be performed using the safety analysis set. The safety analysis set comprises all IMP-treated patients and are analysed according to the actual treatment received.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

List of Abbreviations

ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical (Classification System)
CCC	Clinical Coordinating Centre
CCL	CC Chemokine Ligand
COPD	Chronic Obstructive Pulmonary Disease
CSF	Colony-stimulating Factor
CVP	Central Venous Pressure
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Emergency Department
EQ-5D-5L	EuroQoL group's 5-dimension 5-level Questionnaire
EudraCT	European Union Clinical Trial Database
EVLW	Extravascular Lung Water
FAS	Full Analysis Set
FiO_2	Fraction of Inspired Oxygen
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCO_3	Bicarbonate
ICMJE	the International Committee of Medicinal Journal Editors
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IL	Interleukin
IMP	Investigational Medicinal Product
IND	Investigational New Drug

IRB	Institutional Review Board
ITT	Intention-to-Treat
KM	Kaplan Meier
LOCF	Last Observation Carried Forward
LPLV	Last Patient Last Visit
LTA	Lymphotoxin Alpha
MAP	Mean Arterial Pressure
MedDRA	Medical Dictionary for Regulatory Activities
P&VFD	Vasopressor- and Mechanical Ventilator-free Day
$PaCO_2$	Arterial Carbon Dioxide Partial Pressure
PaO_2	Arterial Oxygen Partial Pressure
PK	Pharmacokinetic
PP	Per Protocol
PPI	Pulmonary Permeability Index
PT	Preferred Term
QALY	Quality-adjusted Life Years
RRT	Renal Replacement Therapy
SaO_2	Arterial Oxygen Saturation
$ScvO_2$	Central Venous Oxygen Saturation
SOC	System Organ Class
SOFA	Sequential Organ Failure Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee
VEGFA	Vascular Endothelial Growth Factor

Definition of Terms

Audit	A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analysed, and accurately reported according to the protocol, sponsor's standard operating procedures, good clinical practice, and the applicable regulatory requirement(s).
Clinical Coordinating Center	A third party contracted by Ferring to provide support to the trial sites for certain aspects of conduct of the trial, such as assessment of eligibility and medical support.
Compliance	Adherence to all the trial-related requirements, good clinical practice requirements, and the applicable regulatory requirements.
Evaluable Patient	A patient who has been treated with the investigational medicinal product (IMP) and 30 days have passed since initiation of IMP infusion.
Good Clinical Practice	A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected.
Investigator	The person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
Legal Representative	An individual or juridical or other body authorised under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical trial.
Treated Patient	A patient who has been treated with the IMP.
Trial Entry Terms	*Screening* The act of determining if an individual meets requirements for participation in the clinical trial. *Enter (=Consent)* The act of obtaining informed consent for participation in the clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients who have entered into a trial are those who sign the informed consent document directly or through their legally acceptable representatives. *Enrolment (=Randomisation)* The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.

1 INTRODUCTION

1.1 Background

Ferring Pharmaceuticals A/S (hereinafter called Ferring) is currently developing selepressin, a novel vasoconstrictor agent for treatment of patients with vasopressor-dependent septic shock.

Patients suffering from septic shock, defined by the need for vasopressor treatment despite adequate fluid resuscitation, represent an extremely ill patient population with a common need for prolonged intensive care, frequent multisystem organ failure, and a high mortality. Septic shock is one of the most common causes of death in intensive care units (ICUs) and its incidence is rising. The growing incidence is most likely due to increased use of invasive devices and immunosuppressive therapies, higher numbers of immunocompromised patients, more antibiotic resistance, and an aging population.

Selepressin is a cyclic nonapeptide vasopressin analogue with high affinity and selectivity for the human vasopressin V_{1a}-receptor versus the V_{1b}-, V_2-, and oxytocin receptors and no known affinity to other receptors, ion-channels, and transporters (Laporte R et al, 2011). The lack of V_{1b} and V_2 activity is the main differentiator of selepressin from existing vasopressin analogues such as arginine vasopressin.

In addition to its vasopressor activity, one of the key characteristic of selepressin is its apparent anti-leakage properties (Maybauer et al., 2014; Rehberg et al., 2012(a); Rehberg et al., 2011; Su et al., 2012). The ability to limit vascular leakage is a clinically relevant and very important feature of selepressin. While fluid therapy is fundamental to the acute resuscitation of critically ill patients, in those with sepsis accompanied by increased capillary permeability from microvascular injury, it can contribute to tissue oedema and eventually organ dysfunction.

Thus, selepressin may serve a dual role of providing haemodynamic benefit while reducing the leakage of intravascular fluid into the extracellular space. It is believed that these unique characteristics could help address the unmet need in the treatment of vasopressor-dependent septic shock and provide significant benefit for the patients.

Moreover, due to the lack of V_2 activity, selepressin does not cause V_2-mediated antidiuresis and release of coagulation factors (Rehberg et al, 2012(b)), important safety consideration in septic shock patients that often have a positive fluid balance and coagulation disturbances.

1.2 Scientific Justification for Conducting the Trial

Septic shock is characterised by hypotension and decreased tissue perfusion due to vasodilation and capillary leakage. In this setting, vasopressors such as norepinephrine / noradrenaline, epinephrine / adrenaline, and dopamine are considered to be critical life-support necessary to quickly restore perfusion pressure. However, at the same time these drugs may cause serious adverse effects such as arrhythmias, myocardial, mesenteric, cerebral, or digital ischaemia/infarction, and acute kidney

injury. Such complications may prevent or prolong the recovery from septic shock and may cause long-term sequelae. Therefore, interventions that decrease the duration of the need for vasopressors are expected to result in reduced risk of complications and possibly improved patient outcome.

In the first clinical trial with selepressin in septic shock patients (FE 202158 CS02), selepressin reduced the need for norepinephrine/noradrenaline in a dose-dependent manner (Ferring report, CS02). Furthermore, selepressin significantly reduced the duration of mechanical ventilation compared to placebo during the first 7 days. Also, cumulative fluid balance and fluid overload tended to be reduced compared to placebo. However, the FE 202158 CS02 trial was not powered to assess clinical outcomes and therefore, a large pivotal trial is needed to fully assess the effects and clinical outcomes associated with the use of selepressin.

The present trial (trial code: 000133) is an adequately powered Phase 2b/3 clinical trial designed to assess and confirm the efficacy and safety of selepressin as a treatment for patients with vasopressor-dependent septic shock. The trial design has been reviewed by both the United States Food and Drug Administration and the European Medicines Agency.

1.3 Benefit / Risk Aspects

Selepressin is a potent vasoconstrictor and expected pharmacological effects include correction of hypotension which makes treatment potentially beneficial to the septic shock patients participating in the trial. The vasoconstrictor effect of selepressin has been investigated in a number of studies in vitro and in vivo in healthy animals, in sheep models of severe sepsis and septic shock, in isolated human resistance arteries, and in septic shock patients. In animal models of severe sepsis and septic shock, selepressin was shown to limit fluid accumulation and pulmonary oedema formation (Maybauer et al, 2014; Su et al, 2012). In patients with septic shock, this may provide clinical benefit by reducing mortality and/or the total duration of time that the patient requires life support with vasopressors and mechanical ventilation, speeding up the recovery, and reducing the risk of short- and long-term sequelae from organ dysfunction.

In healthy adult men and women, the safety profile of selepressin was consistent with the pharmacological effects of a V_{1a} agonist, mainly related to its vasoconstrictor properties, and did not cause any safety concerns (Ferring report, FE 202158 CS01). The dose-limiting effect was reduction in cardiac output. The infusion of selepressin was interrupted in 7 out of 10 subjects in the highest dose group (13.1 µg/h [i.e. 3.1 ng/kg/min assuming 70 kg body weight]) due to a decrease in cardiac output by more than 25%, which was a pre-defined criterion for termination of infusion. No negative renal or hepatic effects were observed. Some subjects reported signs of gastrointestinal discomfort, pallor, and feeling of body temperature change (i.e. signs of effects on the peripheral blood flow). The ECG, blood gases, lactate, and the other safety laboratory parameters were not affected to any measurable extent by the infusion of selepressin. QTcF values of >450 msec, or an increase of >30 msec, were sporadically observed in all dose groups at all time-points, including 7 subjects that received placebo. V_{1a}-induced mesenteric vasoconstriction is a general safety concern. However, no signs of mesenteric or myocardial ischaemia were observed in the healthy subjects. The lack of signs of myocardial ischaemia is consistent with previous findings

that selepressin did not demonstrate specific coronary vasoconstrictive properties in anaesthetised dogs.

Two clinical trials in septic shock patients have been conducted. In the first trial (trial code: FE 202158 CS02), selepressin was safe and well tolerated up to an infusion rate of 2.5 ng/kg/min. Too few patients were enrolled in the highest dose group (i.e. 3.75 ng/kg/min), and hence it was not possible to conclude on the safety of this dose level. In approximately 50% of the patients receiving 2.5 ng/kg/min of selepressin, norepinephrine/noradrenaline could be completely weaned within 12 hours whereas all patients receiving 1.25 ng/kg/min required norepinephrine/noradrenaline at 12 hours (Ferring report, FE 202158 CS02). There were neither apparent differences between treatment with selepressin and placebo with respect to adverse event reporting nor apparent shifts or trends in the means of the ECG parameters during the treatment period that could be attributed to the treatment. A number of patients in all treatment groups, including >75% of the placebo patients, had occasional QTcF values >450 ms, several of whom already had this finding at baseline, or an increase of >30 ms. These observations were regarded as caused by the underlying disease.

The second trial in septic shock patients (trial code: 000025) investigated the dose-range from 2.5-7.5 ng/kg/min and allowed free up- as well as down-titration of selepressin within a certain range. Data from this trial showed that: 1) it was possible to wean norepinephrine/noradrenaline completely within few hours in most of the patients when the selepressin dose was increased to 5-7.5 ng/kg/min, 2) it was possible to maintain mean arterial pressure (MAP) within a target range by adjusting the dose, and 3) in the majority of patients, doses above 3.75 ng/kg/min were only needed during the first 6 hours. Five patients reported a total of eight treatment-emergent serious adverse events which were regarded as related to the treatment. Four of these events occurred in the same patient including one with fatal outcome. Although it cannot be ruled out that the infusion of selepressin, which was stopped after 9.5 hours, approximately 17 hours before the fatal outcome, contributed to the development of the adverse event, it should be recognised that the condition of the patient at enrolment was very serious with a very high baseline infusion rate of noradrenaline (1 µg/kg/min) and a high lactate level (5.4 mmol/L).

The pharmacokinetic profile of selepressin in septic shock patients is based on data from the FE 202158 CS02 and the 000025 trials. As the infusion rate of selepressin was adjusted according to the need of the patient, the pharmacokinetic parameters were calculated by means of population pharmacokinetic modelling. Clearance was on average estimated to 11.28 L/h in a typical patient with a body weight of 70 kg, with inter-individual variability of 22 (CV%). The time to steady state concentration was approximately 7 hours and the steady-state concentrations were proportional to the initial infusion rate. The terminal half-life was approximately 1.4 hours irrespective of dose. However, the initial distribution phase half-life was short, approximately 10 minutes.

The evaluation of benefits and risks indicate that participation in this trial is associated with a favourable benefit-risk ratio. The trial is justified by the potential clinical benefit of a selective V_{1a} receptor agonist treatment in patients with vasopressor-dependent septic shock and the risk posed to the patients participating in the trial is deemed low as the standard septic shock treatment will be in

line with the Surviving Sepsis Campaign guidelines (Dellinger et al, 2013). Patients participating in this trial will be closely monitored and they will have either the same or more frequent contacts with treating clinicians compared to routine treatment, depending on local clinical practice.

For further information regarding selepressin, please refer to the current investigator's brochure.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary Objective

- To demonstrate superiority of selepressin plus standard care versus placebo plus standard care in the number of vasopressor- and mechanical ventilator-free days (with penalty for mortality) in patients with vasopressor-dependent septic shock

Secondary Objectives

- To determine the efficacy of selepressin on:
  - Organ dysfunction
  - Morbidity and mortality
  - Fluid balance
  - Health-related quality of life
- To determine the safety profile of selepressin
- To determine the pharmacokinetics of selepressin
- To determine the health economics of selepressin
- To further evaluate a range of biomarkers in relation to the mode of action of selepressin

2.2 Endpoints

Primary Endpoint

- Vasopressor- and mechanical ventilator-free days (P&VFDs) up to Day 30

This composite endpoint is defined as the number of days (reported to one decimal place [0.0 to 30.0 days]) from start of treatment with the investigational medicinal product (IMP) [selepressin or placebo] to 30.0 days thereafter during which the patient is: 1) alive; 2) free of treatment with intravenous vasopressors; and 3) free of any invasive mechanical ventilation (see definition below).

Any patient that dies within this 30-day period is assigned zero P&VFDs, even if there is a period during which the patient is free of both vasopressor treatment and mechanical ventilation. If vasopressors need to be restarted or mechanical ventilation needs to be initiated or restarted, and the use of either is greater than 60 minutes within a 24-hour period, then the clock is reset and the patient is not considered free of vasopressors and/or mechanical ventilation until after those therapies are again finally discontinued. Vasopressor use or mechanical ventilation during - and up to three hours after - surgery / procedure (including bedside) is exempt from this rule (i.e. does not reset the calculation of P&VFDs). The intent is for the endpoint to reflect the speed of recovery from septic shock and respiratory failure, with appropriate penalties for recurrent shock, new or recurrent respiratory failure, and death.

Vasopressor use is defined as any intravenous dose of norepinephrine/noradrenaline, phenylephrine, dopamine, epinephrine/adrenaline, vasopressin, terlipressin, and IMP (i.e. selepressin and placebo).

Mechanical ventilation is defined as use of endotracheal or tracheostomy tube assisted ventilation (>5 cm H_2O continuous positive airway pressure and >5 cm H_2O of pressure support from the ventilator in tracheostomy patients). End of mechanical ventilation is defined as: 1) extubation of intubated patients or 2) ≤5 cm H_2O continuous positive airway pressure and ≤5 cm H_2O of pressure support from the ventilator in tracheostomy patients. If non-invasive ventilation by mask or bag (>5 cm H_2O of pressure support) is deployed to avoid (re)intubation, it also counts as mechanical ventilation. However, all other uses of non-invasive ventilation such as chronic night-time use of positive airway pressure for chronic obstructive pulmonary disease (COPD) or sleep apnea does not count as mechanical ventilation (regardless of pressure).

Key Secondary Endpoints

The following key secondary endpoints have been selected for the purpose of a possible label inclusion (see Section 9.6.3).

- All-cause mortality (defined as the fraction of patients that have died, regardless of cause) at Day 90
- Renal replacement therapy (RRT)-free days up to Day 30 (excluding patients on RRT for chronic renal failure at time of randomisation)

- Intensive care unit (ICU)-free days up to Day 30

Secondary Efficacy Endpoints

Other secondary endpoints are listed below. All ssessments related to the endpoints are described in Section 7.1.

Organ dysfunction

- Vasopressor-free days up to Day 30
- Mechanical ventilator-free days up to Day 30
- Duration of septic shock (i.e. vasopressor use) up to Day 30
- Duration of mechanical ventilation up to Day 30
- Incidence of RRT up to Day 30 (counting patients who die as on RRT and excluding patients on RRT for chronic renal failure at time of randomisation)
- Duration of RRT up to Day 90 (excluding patients on RRT for chronic failure at time of randomisation)
- Daily overall and individual organ (cardiovascular, respiratory, renal, hepatic, coagulation) scores using a modified version of the Sequential Organ Failure Assessment (SOFA) until ICU discharge
- Incidence of new organ dysfunction and new organ failure (based on the SOFA score) up to Days 7 and 30

Morbidity and mortality

- ICU length of stay up to Day 30
- All-cause mortality (defined as the fraction of patients that have died, regardless of cause) at Days 30 and 180

Fluid balance

- Daily and cumulative fluid balance until ICU discharge (for a maximum of 7 days)
- Daily and cumulative urine output until ICU discharge (for a maximum of 7 days)

Health-related quality of life

- Change in utility, based on the EuroQol group's 5-dimension 5-level (EQ-5D-5L) questionnaire, up to Day 180

Safety Endpoints

- Incidence of adverse events (type, frequency, and intensity) with specific emphasis on:
  - Ischaemic events (e.g. myocardial, skin, cerebral, mesenteric, and limb ischaemia)
- Changes in vital signs and safety laboratory variables, including:
  - Number of clinically significant results assessed as unanticipated in the setting of septic shock
- Episodes of hypotension (MAP <60 mmHg for longer than one hour)

Additional Endpoints

- Hospital-free days up to Day 90
- Hospital length of stay up to Day 90
- Patient residence at Day 30, Day 60, Day 90, and Day 180
- Health economic evaluation - to be reported separately according to a pre-specified health economic analytical plan
- Mean arterial pressure (MAP), until ICU discharge (for a maximum of 7 days)
- Norepinephrine/noradrenaline and other vasopressor doses
- Pharmacokinetic response (in a subset of approximately 200 patients) - to be reported separately according to a pre-specified pharmacokinetic analysis plan
- Creatinine clearance
- Ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2 ratio) (in a subset of 100-350 patients)
- Extravascular lung water and pulmonary permeability index (in a subset of 100-350 patients)
- Cardiac output (in a subset of 100-350 patients)
- Cytokines (in a subset of 100-350 patients)
- Angiopoietin-1 and -2 (in a subset of 100-350 patients)

3 INVESTIGATIONAL PLAN

3.1 Overall Trial Design

The overall trial design is a multi-centre, double-blind, randomised, placebo-controlled, two-part adaptive clinical trial. The trial is designed to investigate the efficacy and safety of multiple dosing regimens of selepressin and to confirm the efficacy and safety of one dosing regimen in treatment of adult patients with septic shock requiring vasopressor treatment.

Up to four dosing regimens of selepressin, as described in Table 1, will be investigated in the first part of the trial and the best-performing dosing regimen will be selected for the second part of the trial.

Table 1 Dosing Regimens

	Starting Dose (ng/kg/min)	Maximum Dose (ng/kg/min)	Range (ng/kg/min)
Arm 1	1.7	2.5	0-2.5
Arm 2	2.5	3.75	0-3.75
Arm 3	3.5	5.25	0-5.25
Arm 4	5.0	7.5	0-7.5

3.1.1 Trial Design Diagram

The overall trial design is illustrated in Figure 1. The entire trial duration for an individual patient is up to 6 months (see Section 6).

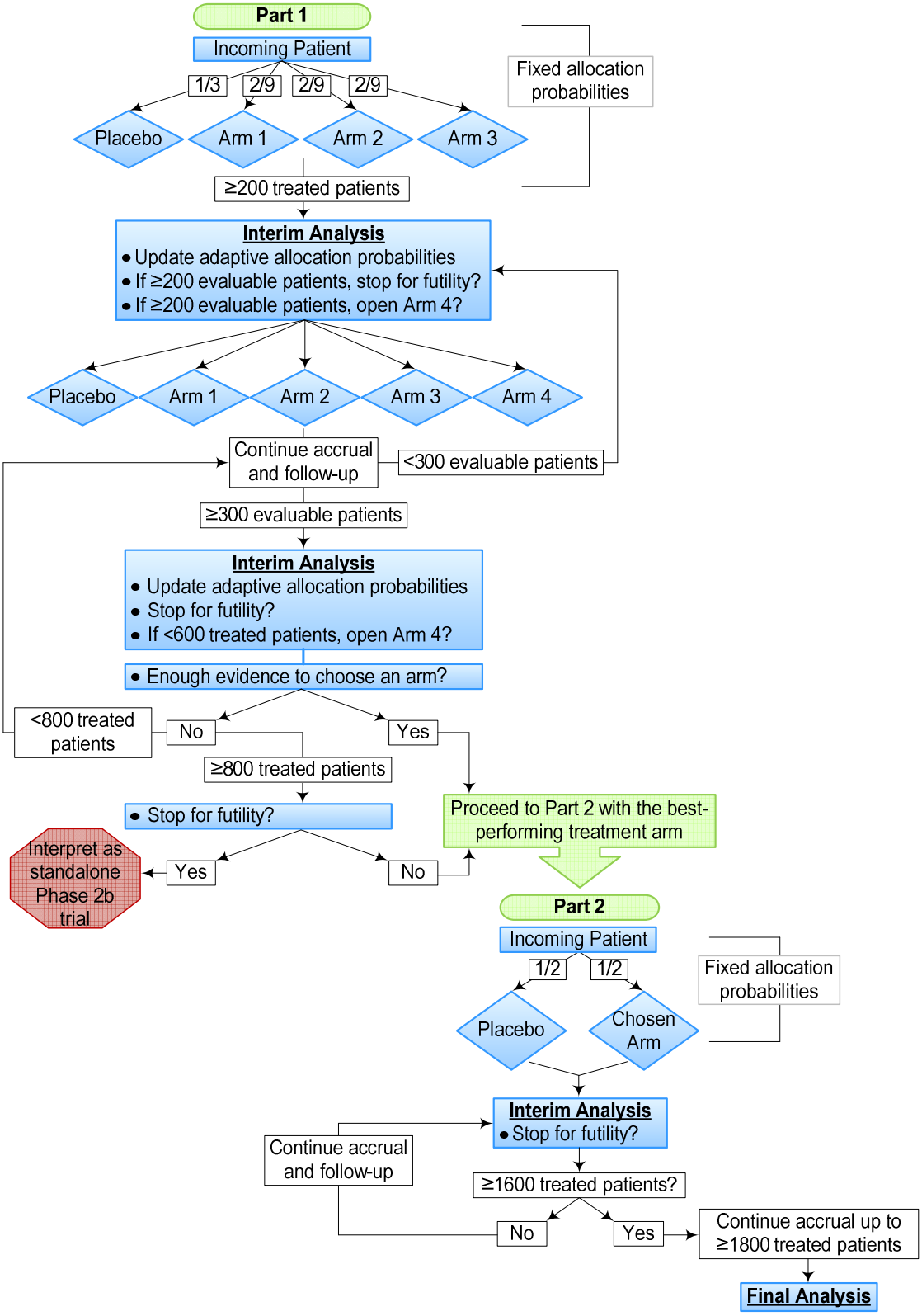


Figure 1 Trial Design

3.1.2 Overall Design and Control Methods

This is a Phase 2b/3 adaptive clinical trial with two parts: Part 1 - Phase 2b and Part 2 - Phase 3 (Figure 1). The entire trial, combining both parts, represents an adequate and well-controlled comparison of selepressin versus placebo. Part 1 comprises 300 evaluable – 800 treated patients. The size of Part 2 will include enough patients to bring the total number of patients in Part 1 and Part 2 to 1800 evaluable patients, ensuring a minimum sample size of 1000 patients in Part 2. The final analysis uses all patients from both parts of the trial.

Part 1 will begin with a 200-patient 'burn-in' period during which fixed randomisation across Arms 1, 2, and 3 will be used (the arms are described in Table 1) with:

- One-third of the patients randomised to placebo
- Two-third of the patients randomised to selepressin (two-ninths of the patients to each of the Arms 1, 2, and 3).

After completion of the 'burn-in' period, Part 1 will utilise response-adaptive randomisation to preferentially allocate patients to the treatment arms that appear to have the maximum benefit with respect to the primary endpoint (i.e. vasopressor- and mechanical ventilator-free days [P&VFD]). A fixed fraction (one-third) of patients will be randomised to placebo throughout Part 1 to ensure contemporaneous control patients are enrolled throughout the trial. Arm 4 will only be opened between 200 evaluable and 600 treated patients and if there is at least a 50% posterior probability that Arm 3 has a higher expected P&VFD than Arm 2 and data from the lower dosing regimens do not suggest any significant safety concerns.

If Part 1 results in the decision to run Part 2, Part 2 will utilise a fixed 1:1 randomisation proportion between placebo and the best-performing dosing regimen of selepressin. The best-performing dosing regimen will be identified at the end of Part 1.

Pre-defined interim analyses will be conducted as described in Section 3.3 and Section 9.9. Patient enrolment will continue without any stop at the interim analyses and a seamless transition to Part 2 can occur after any interim analysis after 300 evaluable - 800 treated patients in Part 1.

3.1.3 Trial Schedule

The estimated timelines are:

- First patient first visit (FPFV): Q3 2015
- Last patient at Day 30 (primary database lock): Q2 2018
- Last patient last visit (LPLV) / end-of-trial: Q4 2018

It is expected that all patients will be recruited within a period of up to 3 years. Hence, the duration of the entire trial is expected to be no longer than 3.5 years.

The primary database will be locked when all ongoing patients have passed Day 30.

3.2 Planned Number of Trial Sites and Patients

Enough patients will be randomised to bring the total number of evaluable patients up to 1800 in the entire trial programme (including both parts of the trial). Patient recruitment will be competitive between trial sites. To achieve the requested number of patients within the given timelines in Section 3.1.3, approximately 60 - 100 trial sites will actively participate in the trial, with additional sites identified as 'back-up' sites to replace non-performing sites.

3.3 Interim Analysis

There will be no interim analyses with the potential to stop the trial early for success. The trial will either stop for futility or run to 1800 evaluable patients.

Once the 'burn-in' period in Part 1 is completed, interim analyses will be conducted regularly during Part 1 to improve the efficiency of dosing regimen selection and to allow early termination for futility or for successful dosing regimen selection.

During Part 2, regular interim analyses for futility will be performed until 1600 patients have been treated.

The interim analyses reports will be prepared by an external company who is not otherwise involved in the conduct of the trial, and who will not divulge these data to Ferring personnel. The measures taken to protect the overall blinding during the interim analyses are illustrated in Figure 2 in Section 5.5.1.

The statistical considerations of the interim analyses are further described in Section 9.9.

3.4 Data and Safety Monitoring Board

A data and safety monitoring board (DSMB) will be established for this trial. The DSMB will be an independent group of critical care and emergency medicine experts not otherwise involved in the trial and a statistician with expertise in adaptive designs. The DSMB will oversee safety and ensure appropriate trial conduct, which includes overseeing that the adaptive design is implemented and performing as intended.

The DSMB will have access to unblinded interim efficacy and safety data as well as recruitment data so that they are able to monitor the enrolment of the intended patient population. The DSMB will keep the interim results confidential from any individuals involved in the trial conduct. A trial-specific DSMB charter specifies the composition of the DSMB and its responsibilities and working procedures.

3.5 Discussion of Overall Trial Design and Choice of Control Groups

3.5.1 Trial Design

This is a multi-centre, randomised, placebo-controlled, double-blind Phase 2b/3 adaptive clinical trial, which will be conducted in accordance with the protocol, good clinical practice, and applicable regulatory requirements.

The trial will be conducted at multiple trial sites predominantly across Europe and North America. High-quality trial sites with shared standards of practice and values will be selected; all trial sites follow the globally accepted Surviving Sepsis Campaign guidelines (Dellinger et al, 2013) which provides recommendations for the best care of patients with severe sepsis and septic shock.

Patients will be enrolled in the trial and the IMP infusion will be initiated as early as possible. To ensure, as far as possible, that only eligible patients enter the trial (see Section 4.1), all potential patients will be discussed with one of the assigned clinical coordinating centres (CCCs) prior to randomisation. The CCCs will be available 24 hours a day throughout the trial to answer investigators' medical questions (such as assessment of eligibility and medical support).

As described in Section 3.4, the trial will be overseen by an independent DSMB. In addition, a trial steering committee (TSC) will oversee the overall conduct of the trial in a blinded manner. The TSC includes representatives of Ferring and the CCCs, trial investigators, and experts in the fields of critical care, emergency medicine and clinical trial methodology. The TSC will make recommendations to Ferring regarding all trial-related decisions including those based on recommendations from the DSMB. A TSC charter specifies the composition of the TSC and its responsibilities and working procedures.

The trial design is robust with clear, prospectively determined clinical and statistical analytic criteria. The design achieves control of type 1 error through analytical means. While the trial can stop early for futility, a successful Phase 3 trial can only be achieved with at least 1800 evaluable patients. At the end of the trial, a single test statistic will be calculated to compare two populations that are defined before the trial begins, namely patients allocated to placebo compared to patients allocated to any dosing regimen of selepressin.

3.5.2 Selection of Endpoints

Mortality is indisputably a critical endpoint to consider in septic shock patients; however, as more and more patients survive septic shock it becomes increasingly important to focus on patient-centred outcomes in survivors such as improving the speed of recovery, the ability to limit the need for life support, and long-term sequelae of septic shock. Therefore in this trial, we will not only assess mortality, but also compare survival free of both vasopressor and mechanical ventilation – the two primary forms of life-support provided to septic shock patients in the ICUs. The primary endpoint is constructed to capture selepressin's ability to hasten the resolution of septic shock and to reduce the time the patient is dependent on life-support. A faster resolution of septic shock is expected to lead to a reduction in irreversible morbidities and serious outcomes resulting from fluid overload and ischaemic damage to organs.

The primary endpoint is a composite endpoint capturing the need for vasopressor, the need for mechanical ventilation, and mortality. All three components on their own represent important beneficial effects for septic shock patients and will also be captured separately as secondary endpoints. This combined endpoint (vasopressor- and mechanical ventilator-free days [P&VFDs])

is well aligned with the currently understood beneficial actions of selepressin and supported by the effects of selepressin found in previous non-clinical and clinical trials as discussed in Section 1.

Septic shock is associated with a wide array of serious and troublesome sequelae that may impact long-term outcomes. The secondary efficacy and safety endpoints (as listed in Section 2.2) were selected to focus on key effects related to the primary mode of action of selepressin (i.e. vasopressor and anti-leakage effects) and at the same time to capture other clinically meaningful outcomes such as incidence of organ dysfunction, mortality, quality of life, and general safety of selepressin. Hence, the secondary endpoints will capture both efficacy and safety aspects of the treatment. Furthermore, the length of stay at the ICU as well as health-related quality of life represent society and life impact focused endpoints.

Patients with septic shock represent a notoriously heterogeneous patient population. To account for potential differences in outcome based on baseline characteristics, patients will be randomised in a stratified manner as described in Section 4.2.2.

3.5.3 Choice of Control Group

In this trial, selepressin plus standard of care will be compared to placebo plus standard of care with norepinephrine/noradrenaline as primary vasopressor. Use of placebo allows provision of usual standard of care in both the selepressin-treated group and the placebo-treated group. The investigators can continue the use of norepinephrine/noradrenaline, continue to add (or not) antibiotics, fluids, inotropic agents (such as dobutamine), oxygen, mechanical ventilation, corticosteroids, feeding, and other supportive care in accordance with standard clinical practice following the Surviving Sepsis Campaign guidelines (Dellinger et al, 2013). Thus, this background of ethical usual clinical care would occur in both the selepressin-treated group and the placebo-treated group.

3.5.4 Selection of Doses in the Trial

Four dosing regimens of selepressin ranging from 1.7 ng/kg/min to 7.5 ng/kg/min (as detailed in Table 1) have been selected for this trial. These dosing regimens are chosen to cover the relevant dose range based on dosing experience from the previous clinical trials (i.e. FE 202158 CS02 and 000025).

In FE 202158 CS02, which was the first clinical trial in septic shock patients, selepressin was safe and well tolerated up to 2.5 ng/kg/min. In approximately 50% of the patients receiving 2.5 ng/kg/min of selepressin, norepinephrine/noradrenaline could be completely weaned within 12 hours whereas all patients receiving 1.25 ng/kg/min of selepressin required norepinephrine/noradrenaline at 12 hours (Ferring report FE 202158 CS02). This suggests that some patients may require more than 2.5 ng/kg/min of selepressin in order to wean norepinephrine/noradrenaline completely.

The second clinical trial (000025) was initiated to assess whether use of higher doses of selepressin would allow for a faster and more complete weaning of norepinephrine/noradrenaline. In that trial,

the dose-range from 2.5 to 7.5 ng/kg/min with free up- and down-titration of selepressin within a certain range was investigated. The flexible dose-adjusting was designed to mimic the current clinical practice for the use of vasopressors. The 000025 trial showed that it was possible to wean norepinephrine/noradrenaline completely within a few hours in most of the patients when the selepressin dose was increased to 5 to 7.5 ng/kg/min. Despite the pharmacokinetic characteristics of selepressin (i.e. approximately 7 hours to reach steady state plasma levels and a half-life of approximately 1.4 hours), it was possible to maintain MAP within the target range by adjusting the dose. In the majority of patients, doses above 3.75 ng/kg/min were only needed in the first 24 hours. However, as the 000025 trial was not designed (or powered) to provide data on efficacy and safety, it is not known whether allowing the use of higher doses of selepressin is associated with an increased benefit or safety risk; hence, four dosing regimens (see Table 1) have been selected for investigation in the 000133 trial.

The lowest dosing regimen selected for the 000133 trial is expected to allow partial weaning of norepinephrine/noradrenaline and will address the question whether low doses of selepressin or co-treatment of selepressin and norepinephrine/noradrenaline is superior to full substitution of norepinephrine/noradrenaline with selepressin. The higher dosing regimens will allow progressively faster and more complete weaning of norepinephrine/noradrenaline and will answer the question whether higher doses of selepressin are associated with increased clinical benefit. The high granularity in the dose-selection is chosen to increase the ability to detect the dosing regimen that provides the optimal risk-benefit ratio.

3.5.5 Selection and Timing of Dose for Each Patient

Treatment with the IMP (selepressin or placebo) has to start as early as possible following fulfilment of the eligibility criteria and no later than 12 hours after initiation of the required continuous infusion of vasopressor treatment for septic shock. All patients will be on norepinephrine/noradrenaline treatment as part of standard of care at the time when the IMP infusion is initiated.

During the course of treatment, the IMP will be continuously administered and adjusted within pre-defined infusion rates. An administration guide will be provided with recommendations on how to adjust the IMP infusion rate.

As the vasopressor-need varies significantly from patient to patient and over time in any given patient, it is necessary to allow dose-adjustments. A lower starting infusion rate of the IMP has been included to minimise the risk of overshooting when IMP is added on top of the norepinephrine/noradrenaline infusion the patient is receiving to maintain the target MAP. The infusion rate of the IMP will be increased if the starting rate is insufficient to wean norepinephrine/noradrenaline completely. If the MAP is increased above the target, norepinephrine/noradrenaline will be weaned first while aiming to keep MAP at the target. Norepinephrine/noradrenaline must be completely weaned prior to weaning of the IMP. If the IMP alone increases the MAP above the target, the IMP will be weaned step-wise while aiming to keep MAP at the target. If the maximum allowed infusion rate of the IMP is not sufficient to maintain the MAP at the target, norepinephrine/

noradrenaline will be added to achieve the targeted MAP. If target MAP cannot be maintained despite maximum allowed infusion rate of IMP and ≥1 µg/kg/min norepinephrine/noradrenaline base (or a total catecholamine equivalent of 1 µg/kg/min norepinephrine/noradrenaline base), vasopressin may be added.

The IMP infusion will continue as long as blood pressure support is deemed necessary with a maximum of 30 days. After complete weaning, IMP infusion may be re-started during this 30-day period for treatment of sepsis-induced hypotension if there is no suspicion of mesenteric or cardiac ischaemia. Patients who still need vasopressor treatment after 30 days will be switched to other vasopressors at the discretion of the investigator.

4 SELECTION OF TRIAL POPULATION

4.1 Trial Population

The intention is to enrol a typical sample of patients presenting with septic shock and commence treatment with the IMP during the initial hours of resuscitation, within 12 hours from the onset of vasopressor treatment, targeting those who do not respond rapidly to fluids and whose vasopressor-need persists for at least one hour.

4.1.1 Inclusion Criteria

1. 18 years of age or older.

2. Proven or suspected infection.

3. Septic shock defined as hypotension (systolic blood pressure less than 90 mmHg OR MAP less than 65 mmHg) requiring vasopressor treatment (i.e. any dose of norepinephrine / noradrenaline base greater than 5 µg/min) despite adequate fluid resuscitation (at least one litre for hypotension).

   The MAP threshold for inclusion in the trial is a MAP below 65 mmHg before vasopressor support is started. However, it is not a requirement that patients are under the target MAP during vasopressor treatment with norepinephrine/noradrenaline. The patients must require vasopressor treatment to stay on the target MAP i.e. a patient can be at the target of 65 mmHg or higher while on at least 5 µg/min of norepinephrine/noradrenaline base at least for one hour before inclusion and when IMP is started.

   A patient can also be included based on systolic blood pressure less than 90 mmHg even if the MAP is above 65 mmHg if the patient is judged in need of vasopressor treatment based on evidence of poor organ perfusion.

   The requirement of at least one litre of fluid for hypotension to start the randomisation process balances the need to ensure that patients have been properly fluid resuscitated while still allowing for early enrolment before there is marked endothelial injury and increased permeability so that the proposed permeability-protection of selepressin can be assessed. Fluid resuscitation should continue according to the recommendations in the Surviving Sepsis Campaign guidelines (Dellinger et al, 2013) and therefore the patients should have received the recommended 30 mL/kg fluid from the onset of hypotension and to the time IMP infusion is started (unless evidence of fluid replete/overload) (see Section 4.1.3).

4. Informed consent obtained in accordance with local regulations.

4.1.2 Exclusion Criteria

1. Not possible to initiate IMP treatment within 12 hours from onset of vasopressor treatment for septic shock.

   Patients will be excluded if IMP infusion cannot be started within 12 hours from onset of vasopressor treatment. This time limit exclusion is added to ensure that patients are included early in the septic shock state. If the inclusion is left too late, then there is often irreparable organ dysfunction and endothelial injury with increased permeability in septic shock. Thus, even an effective intervention could fail if applied later when there is irreversible injury.

2. Primary cause of hypotension not due to sepsis (e.g. major trauma including traumatic brain injury, haemorrhage, burns, or congestive heart failure/cardiogenic shock).

3. Previous severe sepsis with ICU admission within this hospital stay.

   Patients who have had a prior episode of severe sepsis have a poorer prognosis and may still be recovering from the associated organ dysfunction so patients with previous severe sepsis within this hospital stay are not eligible.

4. Known/suspected acute mesenteric ischaemia.

   Selepressin is a potent V_{1a} agonist and V_{1a}-induced mesenteric vasoconstriction is a safety concern so patients with known or suspected acute mesenteric ischaemia are not allowed for safety reasons.

5. Suspicion of concomitant acute coronary syndrome based on clinical symptoms and/or ECG during this episode of septic shock.

   V_{1a} agonism could also induce coronary vasoconstriction and so, for safety reasons, patients are not allowed in the trial if the investigator believes the ECG and clinical symptoms suggest a concomitant acute coronary syndrome.

6. Chronic mechanical ventilation for any reason OR severe COPD requiring either continuous daily oxygen use during the preceding 30 days or mechanical ventilation (for acute exacerbation of COPD) during the preceding 30 days.

   A potential confounder to interpretation of the efficacy of selepressin on ventilator-free days would be inclusion of patients who have severe COPD requiring chronic oxygen use or mechanical ventilation. Such patients may recover from the acute pulmonary effects of septic shock (such as acute respiratory distress syndrome) because of the proposed beneficial effects of selepressin but then prove difficult and slow to wean from mechanical ventilation because of their significant underlying disease. Accordingly such patients are not allowed in the trial. However, patients with less severe COPD are allowed.

7. Received bone marrow transplant during the preceding 6 months or chemotherapy during the preceding 30 days for lymphoma or leukemia.

   Patients who have had bone marrow transplant during the preceding 6 months or chemotherapy during the preceding 30 days for lymphoma or leukemia are excluded because these patients can have a significantly worse prognosis compared to the average septic shock patient due to their impaired immunity and other effects of their underlying disease and its treatment. Depending on the state of immune dysfunction, the mortality rate of these patients when they get septic shock - even with aggressive intensive care, resuscitation, and appropriate intravenous broad spectrum antibiotics - can exceed 90%. Furthermore, many of these patients have thrombocytopenia secondary to their disease or their therapies and this underlying thrombocytopenia increases the risks of worsening to profound thrombocytopenia during septic shock because septic shock induces thrombocytopenia directly and independent of prior chemotherapy. Finally, many of these patients have other mortality risk factors such as anemia, hepatic and renal dysfunction, all of which would be worsened during septic shock.

8. Known to be pregnant.

9. Decision to limit full care taken before obtaining informed consent.

10. Use of vasopressin in the past 12 hours prior to start of the IMP infusion or use of terlipressin within 7 days prior to start of the IMP infusion.

11. Prior enrolment in the trial.

12. Prior use of an investigational medicinal product within the last month OR planned or concurrent participation in a clinical trial for any investigational drug or investigational device.

    In order to be able to assess the safety and efficacy of selepressin without confounding factors from the use of other investigational drugs or devices, co-enrolment in trials involving investigational products are not allowed. Co-enrolment in a non-investigational trial requires preapproval of the TSC and will be assessed on a case by case basis. In principle, co-enrolment is allowed unless it is expected to impact the outcome of this clinical trial.

4.1.3 Eligibility Criteria – Post-randomisation / Before Start of IMP Infusion

In addition, the following criteria must be met at start of IMP infusion:

1. Received a minimum of 30 mL/kg fluid in total from the onset of hypotension (or less if evidence of fluid replete/overload).
2. Received a continuous infusion of norepinephrine/noradrenaline base greater than 5 µg/min for at least one hour and is still receiving at least 5 µg/min norepinephrine/noradrenaline base.

The requirement of at least one hour duration of vasopressor support is intended to ensure a certain severity of the septic shock while balancing the need to recruit patients early during the initial hours of resuscitation.

3. Less than 12 hours since onset of vasopressor treatment for septic shock.

4.2 Method of Assigning Patients to Treatment Groups

4.2.1 Recruitment

Both emergency departments (EDs) and ICUs will recruit patients. Each patient considered for the trial will receive a unique screening number. The screening number will be allocated sequentially within each trial site in the order in which the patients are screened. The screening number and the result of each screening will be recorded.

A screening log with patient identification details for consecutive patients with septic shock must be maintained at each trial site to capture how many patients that were screened to include the 1800 evaluable patients in the trial. The main reason for exclusion will be described.

4.2.2 Randomisation

A computer-generated randomisation list will be prepared prior to enrolment of the first patient into the trial and updated during the trial via the response-adaptive randomisation procedure.

To minimise the risk of imbalance between the treatment arms, the randomisation will be stratified by: 1) trial site, 2) need for mechanical ventilation (‘Yes’ or ‘No’), 3) norepinephrine/noradrenaline requirement (< or ≥30 µg/min), and 4) plasma/serum creatinine (< or ≥150 µmol/L).

The patient-specific randomisation number will be allocated in the order at which the patients are being randomised into the trial. The actual patient randomisation number will be added on the screening log. No patient can be enrolled twice.

The first 200 patients will be randomised to treatment in a fixed manner. The randomisation is 3:2:2:2:0 for placebo and active treatment arms 1, 2, 3, and 4, respectively. After the first 200 patients and throughout the rest of Part 1, the patients will be randomised with one-third probability to placebo and the remaining probability allocated to active treatment arms in a response-adaptive randomisation manner. A pre-defined algorithm will be used to determine the relative randomisation to each of the treatment arms. Interim analyses will be conducted regularly in Part 1 to adjust the adaptive randomisation probabilities for the active treatment arms. The enrolment of patients will continue without any stop at the interim analyses.

During Part 2, a minimum of 1000 patients will be randomised in a 1:1 fashion to placebo and the active treatment arm selected from Part 1 in order to get the 1800 evaluable patients needed for the final analysis.

4.3 Restrictions

4.3.1 Prior and Concomitant Medications/Procedures

Medicinal products may be administered and concomitant procedures may be conducted for the well-being of the patients at the discretion of the investigators.

Use of vasopressors, mechanical ventilation, RRTs, and fluids must be documented thoroughly as these are related to the endpoints of the trial (see Section 2.2). Concomitant medications/procedures that are likely to influence the outcome from septic shock have to be detailed.

4.3.2 Prohibited Medications/Procedures

The following medications/procedures are prohibited:

- Vasopressin in the past 12 hours prior to start of IMP infusion and during IMP infusion unless the patient remains hypotensive despite the maxium allowed infusion rate of IMP and ≥1 µg/kg/min norepinephrine/noradrenaline base (or a total catecholamine equivalent of 1 µg/kg/min norepinephrine/noradrenaline base).
- Terlipressin (from 7 days prior to start of IMP infusion to end of ICU stay).
- Another investigational medicinal product (from 1 month prior to trial enrolment to 30 days after initiation of IMP infusion).
- Participation in another clinical trial for an investigational drug or investigational device or co-enrolment in a non-investigational trial that is not pre-approved by the TSC (from 1 month prior to trial enrolment to 30 days after initiation of IMP infusion).

4.4 Discontinuation and Withdrawal

For all discontinuations and withdrawals, the investigator will document the date of the termination and the main reason.

Premature discontinuation of IMP infusion

The IMP infusion will continue as long as blood pressure support is deemed necessary (up to a maximum of 30 days). Premature discontinuation of IMP infusion is defined as termination of IMP infusion even though continued intravenous vasopressor treatment for blood pressure support is needed. A premature discontinuation of IMP infusion may occur if the investigator decides that IMP infusion should be discontinued or if the patient, the patient's legal representative, or attending physician requests that IMP infusion be discontinued. If the IMP infusion is prematurely paused or discontinued due to a serious adverse event, an additional blood sample will be collected (see Section 7.2.2).

Patients whose IMP infusion is prematurely discontinued, regardless of reason, are not discontinued from the trial. These patients will continue in the trial and undergo the trial assessments following the trial protocol in order to provide the data needed for the analyses and to determine their survival status.

If a patient who does not meet the eligibility criteria is inadvertently enrolled and the IMP infusion has been started, the investigator will consult with the CCC regarding termination or continuation of the IMP infusion.

Withdrawal from the trial

A patient has the right to withdraw from the trial at any time for any reason, without the need to justify the decision.

In the event that the patient (or the patient's legal representative) withdraws consent or the investigator or Ferring, for any reason, prematurely stops the patient's participation in the trial, the IMP infusion and all scheduled trial-related assessments and laboratory testings will be stopped. Data collected up to withdrawal will remain in the database but data obtained after the patient has withdrawn his/her consent will not be entered into the database. However, results from assessments and blood samples collected prior to the withdrawal of the consent but not analysed at the time of the withdrawal will be entered into the database unless the patient refuses. The patient can request destruction of samples which would otherwise have been kept in storage.

Refer to Section 12.3 for information regarding premature trial termination.

5 TREATMENTS

5.1 Treatments Administered

5.1.1 Investigational Medicinal Product (IMP)

The IMP (selepressin and placebo) will be administered through a central venous catheter as a continuous intravenous infusion at a controlled flow rate using a syringe pump or an infusion pump suited for vasopressor administration. The administration is discussed in Section 3.5.5. A detailed IMP and vasopressor administration guide will be provided to the trial sites.

5.1.2 Norepinephrine/Noradrenaline

In order to be eligible for the trial, all patients will be on norepinephrine/noradrenaline treatment as part of standard of care (see Section 4.1.1). During the trial, the norepinephrine/noradrenaline treatment will continue as deemed necessary. Norepinephrine/noradrenaline will be from the commercial batches that the trial sites are using as part of usual clinical care and no modification to their commercial state will be made.

5.2 Characteristics and Source of the IMPs

Selepressin

Selepressin 0.3 mg/mL is a concentrate for solution for infusion. It has been manufactured in accordance with the principles of Good Manufacturing Practice (GMP) and will be provided by Ferring in vials in which the drug substance has been dissolved in an isotonic 10 mM acetate buffer of pH 4.0.

The concentrate will be diluted with sterile 0.9% sodium chloride solution to one of four different concentrations as detailed in a dilution protocol. Sterile 0.9% sodium chloride solution will be provided together with the vial with selepressin concentrate. The dilution will be prepared by dedicated and trained personnel at the hospital pharmacy or at another approved facility at the hospital. A dilution log will be provided in which the dilution will be documented.

Placebo

Sterile 0.9% sodium chloride solution will be used as the placebo. It will be provided by Ferring from commercial batches and no modification to their commercial state will be made.

5.3 Packaging and Labelling

Packaging and labelling of the IMPs (selepressin and placebo) will be performed under the responsibility of the IMP department at Ferring in accordance with GMP and national regulatory requirements.

The IMPs (selepressin and placebo) will be labelled with trial-specific labels and the content on the labels will be in accordance with Annex 13, EudraLex, volume 4 and national requirements. The labels will contain a self-adhesive tear-off portion to be affixed to the dispensing log maintained at the trial site.

5.4 Conditions for Storage and Use

The IMPs will be stored in accordance with the label.

The investigator will ensure that the IMPs will be stored in appropriate conditions in a secure location with controlled access. The storage compartment shall be monitored regularly and the temperature shall be documented. Deviations in storage temperature must be reported to Ferring without delay and the IMPs must not be used until further instructions are received.

Diluted IMP dosing solutions must be used within 26 hours after the preparation if prepared in controlled and validated aseptic conditions, otherwise within 24 hours after the preparation.

5.5 Blinding / Unblinding

5.5.1 Blinding

This is a double-blind, placebo-controlled trial in which patients, investigators and other trial site staff, the CCCs, the TSC, the clinical trial team at Ferring and its representatives will be blinded to the treatment assignment. As discussed in Section 3.4, the DSMB will have access to unblinded data during the trial. The personnel preparing the IMPs and the drug accountability monitors will also be unblinded. Figure 2 illustrates the applicable safeguards to maintain the overall blinding during conduct of trial. Three independent parties will be involved in forming the safeguard during the adaptive portion of the trial. One part (the randomisation company) will provide the expertise to run the adaptive algorithm. The second part (the statistical consulting company) will provide expertise in producing the DSMB reports and provide statistical and project management support for the DSMB. The third part (the adaptive design company) will provide expertise in adaptive clinical trial design to oversee the performance of the adaptive algorithm and provide statistical support for the DSMB in relation to the adaptive trial design.

Adequate blinding of the treating investigators and nurses is important to ensure the integrity of the results. Use of placebo will ensure effective blinding due to the significant individual variability in the vasopressor need from patient to patient. Thus, in some patients the vasopressor need declines quickly and it will not be possible to tell whether fast weaning of norepinephrine/noradrenaline is due to the fact that the patient receives active treatment or whether it is just because the patient is improving. Also, the potential side effects of selepressin are similar to side effects that can be seen with norepinephrine/noradrenaline or that may be caused by worsening of septic shock so there are no obvious effects of selepressin that will lead to unblinding.

The IMPs will be prepared in accordance with the trial-specific computer-generated randomisation numbers. The randomisation will be securely kept without access for personnel involved in the conduct of the trial with exception of the personnel preparing the IMPs until the trial database is declared clean and released to the trial team statistician. The prepared IMPs (i.e. the four diluted selepressin dosing solutions and the placebo) will be indistinguishable i.e. identical appearance and smell and will be administered using similar infusion rates.

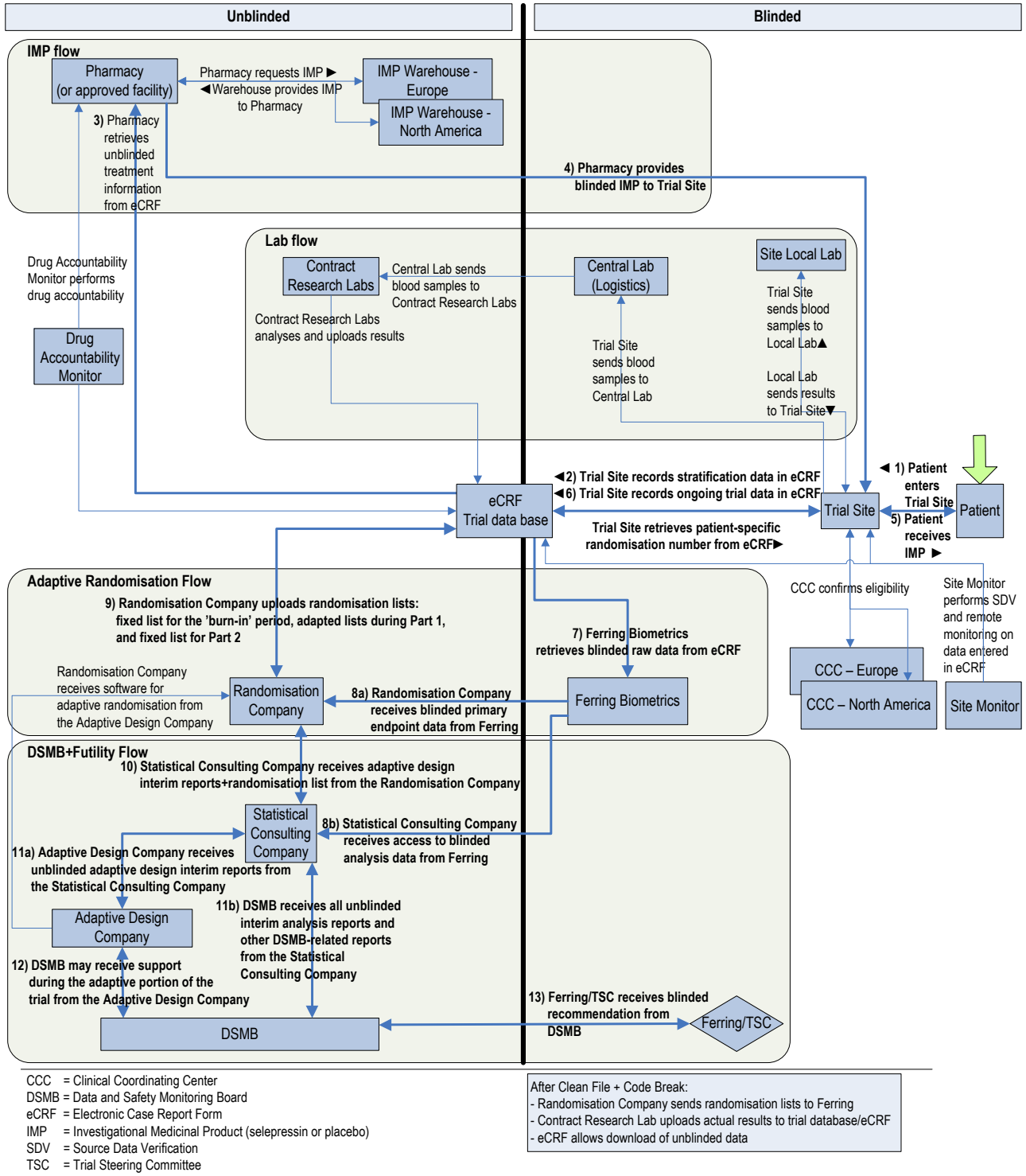


Figure 2 Safeguards to Maintain Blinding during Trial Conduct

5.5.2 Unblinding of Individual Patient Treatment

An emergency decoding possibility (via the eCRF) will be available to the investigator and designated persons at Ferring. Breaking of the blind for individual patients in emergency situations is an investigator responsibility. As far as the emergency permits, the need to break the blind will be discussed with the CCC and communicated to Ferring.

The unblinding in emergency situations is only permitted in case of a suspected unexpected serious adverse reaction (SUSAR) or in case of an important adverse event where the knowledge of the medicinal product in question is required for therapeutic decisions for the management of the patient. It will be documented in the eCRF that the code is broken, when, and by whom. The investigator must record the event of unblinding in the patient's medical record, including the reason for unblinding, but not the treatment allocation if this can be avoided.

In case of accidental unblinding, the same documentation as for emergency unblinding must be obtained.

It may be necessary to unblind an individual patient's treatment for the purposes of expedited reporting to the authorities and/or independent ethics committees (IECs) / institutional review boards (IRBs). In that situation, every effort will be made to maintain blinding of personnel involved in data analysis and interpretation. Other personnel may be unblinded for SUSARs, including trial site staff as well as staff acting on behalf of Ferring.

Information on whether the blind has been broken for any patients must be collected before the database is declared clean and released to the trial team statistician.

5.6 Treatment Compliance

The IMPs will only be administered by authorised staff at the trial sites to patients who meet the eligibility criteria and are randomised to a treatment in the trial. The investigator (or his/her designated personnel, e.g. trial nurse) will maintain a drug dispensing log detailing the dates and quantities of IMP administered to, and used by, each patient, as well as the unique batch identifier used in the trial.

The tear-off portion of the labels will be affixed to the drug accountability form. The monitors will verify the drug accountability during the trial.

5.7 Return and Destruction of IMP

All used IMP will be destructed at the trial site in accordance with local requirements after the drug accountability has been finalised, verified by the monitor, and signed off by the investigator. Any material used for preparation of the infusion solution and for the infusion will be destroyed at the trial site immediately after usage according to standard procedures at the trial site.

All unused IMP will be accounted for and must be destructed in a certified way in accordance with trial-specific instructions.

6 TRIAL PROCEDURES

Participating sites should consider all septic shock patients for inclusion in the trial; the main reason for not being eligible will be documented. Refer to Section 4.1 for inclusion, exclusion, and eligibility criteria. One of the assigned CCCs must be contacted to confirm the eligibility of each patient.

The trial consists of a pre-IMP treatment period, an IMP treatment period, and a follow-up period (see Section 6.1).

The pre-IMP treatment period is defined as the time from sepsis-induced hypotension to the start of IMP infusion. To ensure start of IMP treatment without delay, informed consent will be obtained, in compliance with local regulations, as early as possible. During this period, baseline evaluations will be made.

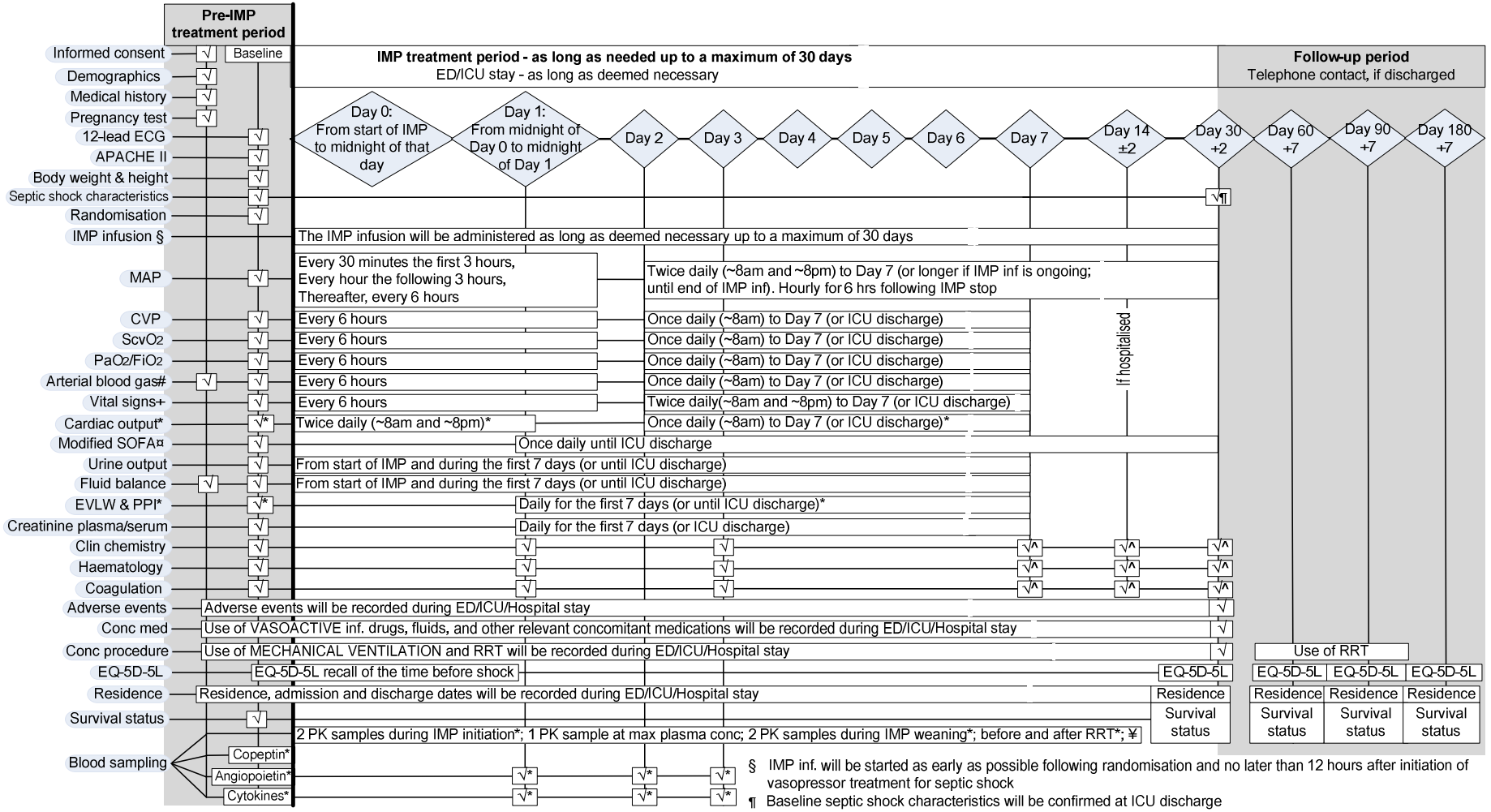
The IMP treatment period begins with Day 0 (which is defined as time from onset of IMP infusion to midnight of that day). The infusion of the IMP (selepressin or placebo) will be started as early as possible following randomisation and no later than 12 hours after initiation of continuous infusion of vasopressor treatment for septic shock. During the course of treatment, the IMP infusion rate will be adjusted as within pre-defined infusion rates to keep the MAP at the target. The IMP administration is described in Section 3.5.5 and the target MAP is defined in Section 7.1.11. A detailed IMP and vasopressor administration guideline will be provided to trial sites. The IMP infusion will continue as long as blood pressure support is deemed necessary with a maximum period of 30 days. A confirmation of the septic shock characteristics recorded at time of enrolment will be recorded in the eCRF at ICU discharge.

The follow-up period includes Days 30, 60, 90, and 180. If a patient has been discharged from the trial hospital, trial site personnel will contact the patient, the patient's legal representative, or the patient's health care professional to collect required trial information.

All assessments to be performed and all data to be collected during the trial are summarised in Section 6.1 and further described in Section 7. The majority of the assessments are widely and routinely used clinically and generally regarded as reliable, accurate, and relevant. Collection of data requiring invasive equipment or mechanical ventilation is applicable only if it is measured as part of local clinical practice. Samples collected and assessments performed for clinical purposes in accordance with standard of care after start of fluid resuscitation for hypotension and before start of IMP may be used as baseline values if deemed appropriate. In case several values of the same assessment are available, the recordings obtained closest to the start of IMP treatment will be used as baseline and the recordings obtained closest to a given time-point will be used as post-baseline values (if not otherwise specified).

At pre-selected trial sites, additional data collection will be performed to further evaluate the effect of selepressin.

6.1 Trial Flow Chart



§ IMP inf. will be started as early as possible following randomisation and no later than 12 hours after initiation of vasopressor treatment for septic shock
¶ Baseline septic shock characteristics will be confirmed at ICU discharge
* Only applicable for patients at pre-selected trial sites
^ Only applicable in hospitalised patients
# PaO_2, $PaCO_2$, SaO_2, HCO_3, pH, base excess, and lactate
\+ Diastolic and systolic blood pressure, heart rate, respiratory rate, body temperature
¤ Based on respiratory, cardiovascular, renal, hepatic, and coagulation
¥ A blood sample will be collected if the IMP infusion is prematurely paused or discontinued due to a serious adverse event

7 TRIAL ASSESSMENTS

7.1 Assessments Related to Endpoints

Vasopressor treatment, mechanical ventilation, and mortality are all part of the primary endpoint and it is extremely important to document these variables thoroughly and without delay. If a patient has been discharged from the trial hospital before Day 30, trial site personnel will contact the patient, the patient's legal representative, or the patient's health care professional to collect required information. If the trial site personnel are unable to collect the required information, Ferring should be notified. Completeness of data collection for the primary endpoint will be closely monitored during the conduct of the trial and issues of missing data collection will result in re-training (or termination) of trial sites.

7.1.1 Vasopressors

The integrity of the primary endpoint depends on accurate start and stop times of vasopressor treatment and therefore start and stop time of all vasopressor periods must be recorded in the eCRF. It is key to ensure that vasopressor treatment is neither prolonged longer than necessary nor prematurely stopped leading to episodes of hypotension.

All vasopressor treatment (any intravenous dose of norepinephrine/noradrenaline, phenylephrine, dopamine, epinephrine/adrenaline, vasopressin, terlipressin, and IMP [selepressin and placebo]) must be thoroughly documented up to Day 30. The infusion rate of IMP will be recorded at baseline and at 1, 3, 6, 12, and 24 hours after start of IMP infusion. After 24 hours, the infusion rate of IMP will be recorded twice daily (around 8:00 a.m. and 8:00 p.m. when the MAP is recorded) until end of IMP treatment. In addition, the IMP infusion rate at the time of pharmacokinetic blood sampling will be recorded in the eCRF. In approximately 200 patients at pre-selected trial sites, the IMP infusion rate at 30 minutes after start IMP infusion will also be recorded (see Section 7.2.2). Furthermore, the total volume of infused IMP within the following time periods will be recorded: 0-12 hours, 12-24 hours, and from 24 hours to regular schedule according to clinical practice at each trial site. Thereafter, daily according to local clinical practice. For all other vasopressors, the dose of each vasopressor will be recorded at baseline and at 1, 3, 6, 12, and 24 hours after start of IMP infusion. After 24 hours, the dose of the individual vasopressors will be recorded twice daily (around 8:00 a.m. and 8:00 p.m. when the MAP is recorded) until end of vasopressor treatment.

7.1.2 Mechanical Ventilation

Respiratory failure, requiring mechanical ventilation, is a common complication of septic shock. In septic shock patients, it is a key goal of management of ventilation to minimise the duration of ventilation because increased duration of mechanical ventilation increases the risk of nosocomial pneumonia, neuromuscular weakness, and death.

The use of mechanical ventilation (as defined in Section 2.2) must be thoroughly documented up to Day 30. Start and stop time of all mechanical ventilation periods must be recorded in the eCRF.

The weaning of mechanical ventilation will be based on daily spontaneous breathing trials as described in a trial-specific weaning guide. The time and outcome (i.e. success or failure) of each spontaneous breathing trial will be documented in patient's medical records to monitor if a successful spontaneous breathing trial is followed by extubation.

7.1.3 Renal Replacement Therapy (RRT) and Renal Function

Acute kidney injury is a common complication of septic shock. Treatment of acute kidney injury is primarily supportive including RRT (continuous RRT, intermittent haemodialysis, or peritoneal dialysis). The decision to initiate RRT in a patient enrolled in this trial will be based on local clinical practice. The use of RRT must be thoroughly documented up to Day 90. The reason for and type of RRT as well as start and stop time will be recorded in the eCRF. If a patient is shifted from continuous RRT to intermittent haemodialysis, the patient is still on RRT until the last hemodialysis has been performed.

Renal function will be assessed, using urine output, plasma/serum creatinine, and creatinine clearance, at baseline and the first 3 days after initiation of IMP infusion and up to 7 days if collected for clinical purposes [or until ICU discharge if the patient leaves the ICU before Day 7]). Creatinine clearance will be determined by estimated glomerular filtration rate (using plasma/serum creatinine, age, and gender as per Cockcroft-Gault equation).

7.1.4 Modified Sequential Organ Failure Assessment (SOFA) Score

SOFA is a scoring system used to track the patient's organ function status during episodes of critical illness (Vincent et al, 1996).

In this trial, a modified version of the SOFA will be used (i.e. SOFA except the Glasgow Coma Scale). As many patients are sedated due to mechanical ventilation a meaningful assessment of the neurological function using the Glasgow Coma Scale cannot be performed. In addition, any dose of IMP, vasopressin, terlipressin, or phenylephrine will attribute 3 points on the cardiovascular scale, and any dose of the positive inotropes milrinone and levosimendan will attribute 2 points on the cardiovascular scale.

The worst value for each individual organ system (i.e. respiratory, cardiovascular, renal, coagulation, and hepatic) components within the past 24 hours (at baseline and once daily until ICU discharge) will be recorded in the eCRF and the eCRF will calculate the overall modified SOFA score.

7.1.5 Mortality Rate and Hospitalisation

The actual date and time for ED, ICU, and hospital admission and discharge as well as time of death (if applicable) will be recorded. Trial site personnel will visit or contact each patient who is still hospitalised and contact each patient or healthcare professional for patients who has left the hospital to determine survival status and current residence.

Functional status and residence of each patient before the infection leading to this episode of septic shock (baseline) as well as functional/survival status and residence throughout the trial will be recorded by using one of the following alternatives:

- Home, receiving no support
- Home, receiving paid professional support
- Home, receiving unpaid support
- Rehabilitation site/skilled (or unskilled) nursing facility
- Other acute care hospital (including long-term acute care)
- Still in (or readmitted to) trial hospital
- Unknown
- Dead

7.1.6 Health-related Quality of Life

The EuroQoL-5-Dimensions (EQ-5D™) will be used to assess patient's overall health. EQ-5D™ is a standardised instrument in two parts for use as a measure of health outcome; it provides a simple, generic measure of health for clinical and economic appraisal (The EuroQol Group; http://www.euroqol.org). The first part includes five dimensions where the patient will indicate which given statements best describe the health state on the day of questionnaire completion. The second part contains a visual analogue scale (VAS) where the patient will indicate how good or bad his or her own health is on the day of questionnaire completion. The VAS scores range from 0 (worst health state) to 100 (best health state).

The five level version of the instrument will be used in this trial (i.e. EQ-5D-5L).

The baseline value refers to a recall of the time before the infection leading to the septic shock episode and the EQ-5D-5L will be completed as soon as possible after the shock state. A telephone interview will be adequate at Days 30, 60, 90, and 180 if the patient has been discharged. The responses will be entered into the eCRF.

The investigator and/or delegated personnel will receive training and instruction in completion of the questionnaire before enrolment of patients.

Each patient must receive proper training and instruction before use. The investigator or a delegated trial team member will instruct the patient to respond to each question without influence from trial team members or accompanying family or friends and explain that there are no right or wrong answers. Nobody will be allowed to answer or interpret questions for the patient.

7.1.7 Fluid balance, Fluids, and Urine Output

In order to investigate selepressin's effect on fluid balance, it is important to document all fluid administered during this episode of severe sepsis/septic shock including the time (i.e. up to 18 hours) before initiation of the IMP infusion (baseline) and during the first 7 days after initiation

of IMP infusion [or until ICU discharge if the patient leaves the ICU before Day 7]). The period of Day 0 is from the start of IMP infusion to the time of the first regular daily fluid recording according to local clinical practice. Thereafter, daily fluid recordings according to local clinical practice.

The fluid balance (as calculated in accordance with local clinical practice) and the total amount of intravenous fluid and urine output will be recorded in the eCRF. Urine output will be used for assessing renal function (see Section 7.1.3).

7.1.8 Adverse Events

The procedure for collecting and reporting adverse events is described in Section 8.

7.1.9 Safety Laboratory Variables (Clinical Chemistry, Haematology, and Coagulation)

Standard safety laboratory variables will be analysed using standard equipment in accordance with local clinical practice. Accreditation/certification of the laboratories and reference ranges of the laboratory variables will be kept in the trial files. The investigator must document their review of the laboratory results. Any laboratory abnormality should be assessed by the investigator as to whether it constitutes an adverse event (see Section 8.1).

The baseline levels and the results, of the variables as listed in Table 2, obtained 1 and 3 days after initiation of the IMP infusion will be recorded. The results obtained at Days 7, 14, 30 will also be recorded if the patient is still in trial hospital.

Daily creatinine, bilirubin, and platelets values will be used for the SOFA scores (see Section 7.1.4). Creatinine level will also be used for assessing renal function and calculation of creatinine clearance (see Section 7.1.3).

Table 2 Safety Laboratory Variables

Clinical Chemistry	Haematology	Coagulation
Alanine aminotransferase	Haematocrit	Activated partial thromboplastin time
Albumin	Haemoglobin	
Alkaline phosphatase	Platelet count	Prothrombin time / international normalised ratio
Aspartate aminotransferase	Red blood cell count	
Calcium (free or total)	White blood cell count	
Chloride		
C-reactive protein		
Creatine phosphokinase		
Creatinine (plasma or serum)		
Lactate dehydrogenase		
Phosphate		
Potassium		
Sodium		
Total bilirubin		
Troponin (I or T)		
Urea (blood urea nitrogen or blood urea)		

7.1.10 Diastolic and Systolic Blood Pressure, Heart Rate, Respiratory Rate, and Body Temperature

Diastolic and systolic blood pressure, heart rate, respiratory rate, and body temperature will be monitored up to Day 7 (or until ICU discharge if the patient leaves the ICU before Day 7) using standard equipment in accordance with local clinical practice. The baseline values, the values measured every 6 hours after initiation of IMP infusion up to midnight of Day 1 and twice daily (around 8:00 a.m. and 8:00 p.m.) the following days will be recorded in the eCRF. Any abnormality should be assessed by the investigator as to whether it constitutes an adverse event (see Section 8.1).

7.1.11 Mean Arterial Pressure

The MAP will be measured intra-arterially (or non-invasively if an arterial line is not available) using standard equipment in accordance with local clinical practice. The method (intra-arterially or non-invasively) used will be documented in the eCRF.

The infusion rate of the IMP will be adjusted to keep the MAP at the target of 65 mmHg. However, a different target MAP will be accepted, if pre-specified in the eCRF and if appropriate, as judged by the investigator, for the clinical management e.g. in patients with previous hypotension or hypertension (if deemed necessary to maintain adequate organ perfusion). In such case, the target MAP and the reason for why a different target MAP has been chosen will be recorded in the eCRF.

The following MAP values will be recorded in the eCRF:

- Baseline.
- Every 30 minutes during the first 3 hours after initiation of IMP infusion.
- Every hour the following 3 hours.
- Thereafter, every 6 hours up to midnight of Day 1.
- Twice daily (around 8:00 a.m. and 8:00 p.m.) until Day 7 or longer if IMP infusion is ongoing (until end of IMP infusion).
- Every hour for 6 hours following discontinuation of the IMP infusion.

In order to assess that vasopressor treatment is not prematurely stopped leading to episodes of hypotension, the MAP will be recorded hourly for the first 6 hours after complete weaning of IMP and episodes of clinically relevant hypotension (i.e. any period recorded in the hospital/medical source records through routine clinical care where the MAP drops below 60 mmHg for more than one hour) will be recorded in the eCRF detailing the total duration of the episode, the lowest MAP measured during the episode, and the actions taken to correct the hypotension.

MAP is also needed for the SOFA score (see Section 7.1.4).

In addition, in the first patients at each trial site, the MAP should be noted in the patient's medical record at the time when the infusion rate of the IMP or the norepinephrine/noradrenaline is adjusted in order to monitor compliance with the IMP and vasopressor administration guide.

7.1.12 PaO_2/FiO_2 Ratio

PaO_2/FiO_2 ratio will be monitored up to Day 7 (or until ICU discharge if the patient leaves the ICU before Day 7) in accordance with local clinical practice. The baseline value, the values measured every 6 hours after initiation of IMP infusion up to midnight of Day 1 and daily (around 8:00 a.m.) the following days will be recorded in the eCRF.

The PaO_2 and FiO_2 are also needed for the SOFA score (see Section 7.1.4).

7.1.13 Extravascular Lung Water and Pulmonary Permeability Index

The extravascular lung water (EVLW) is the amount of water that is contained in the lungs outside the pulmonary vasculature, that is, in the interstitial and alveolar spaces (Jozwiak et al, 2013). The ratio between the EVLW and the pulmonary blood volume is called the pulmonary permeability index (PPI) which is believed to reflect the permeability of the alveolo-capillary barrier (Monnet et al, 2007). Both EVLW and PPI are useful tools to characterise pulmonary oedema.

EVLW and PPI will be collected at pre-selected trial sites who measure these variables as part of clinical practice. The baseline values and the daily (around 8:00 a.m.) values for the first 7 days after initiation of IMP infusion (or until ICU discharge if the patient leaves the ICU before Day 7), as measured using standard equipment in accordance with local clinical practice, will be recorded if available.

7.1.14 Cardiac Output

Cardiac output will be monitored up to Day 7 (or until ICU discharge if the patient leaves the ICU before Day 7) at pre-selected trial sites who measure cardiac output as part of clinical practice. The baseline value and the values obtained twice daily (around 8:00 a.m. and 8:00 p.m.) for the first 2 days after initiation of IMP infusion and daily (around 8:00 a.m.) for the following days, as measured using standard equipment in accordance with local clinical practice, will be recorded if available.

7.2 Trial-specific Blood Sampling

7.2.1 Copeptin Levels

In patients at pre-selected trial sites, a blood sample will be collected before initiation of the IMP infusion for measurement of baseline levels of copeptin.

7.2.2 Pharmacokinetics

One blood sample for measurement of maximal plasma concentration of selepressin will be collected from all patients at one of the following time points (the one that occurs first): 1) right before first attempt to wean the IMP infusion, 2) after at least 7 hours of IMP infusion at maximal infusion rate, 3) at time of first pause of IMP, or 4) at time of IMP discontinuation.

Moreover, if the IMP infusion is prematurely paused or discontinued due to a serious adverse event, an additional blood sample will be collected at the time of IMP discontinuation or pause for measurement of plasma concentration of selepressin.

The IMP infusion rate at the time of the blood sampling will be recorded in the eCRF.

In approximately 200 patients at pre-selected trial sites, additional blood sampling for analysis of pharmacokinetic parameters will be conducted twice during the initiation of the IMP infusion (at approximately 1-3 hours and 6-9 hours after start of infusion) and twice during the weaning of the IMP infusion (at approximately 1-2 hours and 2-3 hours after stop of infusion). If these patients are on RRT, additional blood sampling will also be performed before and after the RRT. The IMP infusion rate at 30 minutes after start of IMP infusion will be recorded in the eCRF.

7.2.3 Cytokines

The development of septic shock is associated with elevated levels of proinflammatory cytokines (Fjell et al, 2013). Exposure to inflammatory mediators and interaction with leukocytes causes endothelial activation and damage (Aird et al, 2003). Vasopressin has effects on immunity (Russell et al, 2010) and decreases cytokines more than does norepinephrine/noradrenaline (Russell et al, 2013). Selepressin is a potent $V1_a$ agonist that could also have effects on cytokines. Furthermore, cytokine levels in the blood may be predictive of the response to selepressin compared to placebo in septic shock.

In patients at pre-selected trial sites, a blood sample will be collected at baseline (before initiation of IMP infusion) and at the first 3 days after initiation of IMP infusion for analysis of several cytokines e.g. VEGFA (vascular endothelial growth factor), interleukin (IL)-6, IL-2, CCL (CC chemokine ligand)-22, CCL11, LTA (lymphotoxin alpha), CSF (colony-stimulating factor)-2.

7.2.4 Angiopoietins

Angiopoietin-1 and angiopoietin-2 are circulating proteins with opposing roles on the vascular endothelium, i.e. angiopoietin-1 protects against vascular leakage whereas angiopoietin-2 promotes increased vascular permeability.

In patients at pre-selected trial sites, a blood sample will be collected at baseline (before initiation of IMP infusion) and at the first 3 days after initiation of IMP infusion for measurement of angiopoietin-1 and -2 levels.

7.3 Other Assessments

7.3.1 Central Venous Pressure

If central venous pressure (CVP) is measured for clinical purposes (via a central venous catheter using standard equipment in accordance with local clinical practice), the baseline value and the values measured every 6 hours after initiation of IMP infusion up to midnight of Day 1 and a daily (around 8:00 a.m.) value the following days until Day 7 (or until ICU discharge if the patient leaves the ICU before Day 7) will be recorded, if available.

7.3.2 Central Venous Oxygen Saturation

If central venous oxygen saturation ($ScvO_2$) is measured for clinical purposes (via a central venous catheter using standard equipment in accordance with local clinical practice), the baseline value and the values measured every 6 hours after initiation of IMP infusion up to midnight of Day 1 and a daily (around 8:00 a.m.) value the following days until Day 7 (or until ICU discharge if the patient leaves the ICU before Day 7) will be recorded, if available.

7.3.3 Arterial Blood Gases and Lactate Levels

If arterial blood gases and acid/base status (arterial oxygen partial pressure (PaO_2), arterial carbon dioxide partial pressure ($PaCO_2$), arterial oxygen saturation (SaO_2), arterial pH, bicarbonate (HCO_3), base excess) and lactate levels are available, as measured using standard equipment in accordance with local clinical practice, the baseline values and the values measured every 6 hours after initiation of IMP infusion up to midnight of Day 1 and a daily (around 8:00 am) result the following days until Day 7 (or until ICU discharge if the patient leaves the ICU before Day 7) will be recorded. In addition, the highest lactate level obtained after start of vasopressor treatment but before start of IMP will be recorded. If arterial lactate level has not been measured, the venous value can be recorded if available.

PaO_2 will be used for the SOFA (see Section 7.1.4) and the PaO_2/FiO_2 ratio (see Section 7.1.12).

7.4 Demographics and Other Baseline Assessments

7.4.1 Demographics

Demographic data including date of birth, race, and ethnic origin will be recorded.

7.4.2 Septic Shock Characteristics

Baseline septic shock characteristics (including site of infection, cause of infection, and whether the infection was proven or suspected) will be recorded. In addition, a confirmation of the septic shock characteristics recorded at time of enrolment and whether initial antibiotic treatment and source control was adequate will be recorded at ICU discharge.

7.4.3 APACHE II

APACHE II is a classification system which uses a point score based upon initial values of routine physiologic measurements, age, and previous health status to provide a general measure of severity of disease (Knaus et al, 1985). In this trial, the baseline (within the preceding 24 hours before initiation of the IMP infusion) APACHE II score will be recorded to assess the similarity of illness severity at baseline between treatment arms.

7.4.4 Electrocardiography

A 12-lead baseline ECG obtained prior to start of IMP infusion must be available. ECGs obtained for clinical purposes within 48 hours of starting IMP may be used as baseline ECG, provided there is no indication of any change in the cardiac condition. If there is any reason to suspect a change in cardiac condition, a new 12-lead ECG should be obtained prior to initiation of IMP. The purpose of the baseline ECG is to have a status at entry to which later ECGs may be compared, should this become relevant. The ECG should be obtained in accordance with local clinical practice and ECG recordings should capture at least four QRS complexes, i.e. three evaluable RR intervals.

Continuous ECG monitoring will be performed as medically required in accordance with local clinical practice.

7.4.5 Body Weight and Height

The baseline (usual) body weight and height will be assessed in accordance with local clinical practice. The baseline weight will be used for calculation of the infusion rate of IMP and the norepinephrine/noradrenaline dosing.

7.4.6 Medical History

Information about relevant medical history will be collected. The Charlson Comorbidity Index will be used.

7.4.7 Prior and Concomitant Medication/Procedure

Information about relevant concomitant medications/procedures will be collected (see Section 4.3).

7.4.8 Pregnancy Test

Women of child bearing potential will be tested for pregnancy (in accordance with local clinical practice) before initiation of IMP infusion. Urine dipstick pregnancy tests will be provided to the trial sites.

7.5 Handling of Biological Samples

Copeptin, cytokines, angiopoietin-1, angiopoietin-2, and selepressin levels will be measured by contract research laboratories. A detailed description of the sample collection and shipment procedures will be included in a trial-specific laboratory manual. These blood samples will be maintained in storage after the end of the trial. Destruction will take place within one year after last visit/trial-related contact with the last ongoing patient. Bio bank/data protection will be handled in compliance with the national/local regulations.

Handling of all other biological samples will be in accordance with local clinical practice.

8 ADVERSE EVENTS

8.1 Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient participating in a clinical trial. It includes:

- Any unfavourable and unintended sign, symptom or disease temporally associated with the use of the IMP, whether or not considered to be caused by the IMP.
- Adverse events commonly observed and adverse events anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality, vital sign, or finding from physical examination assessed as clinically significant and unanticipated in a setting of septic shock by the investigator. Findings from assessments and examinations done during screening are not adverse events, but are recorded as medical history.
- Accidental injuries, reasons for any change in medication (drug and/or dose), reasons for any medical, nursing or pharmacy consultation, or reasons for admission to hospital or surgical procedures.
- Overdoses and medication errors with and without clinical consequences.

8.2 Collection and Recording of Adverse Events

8.2.1 Collection of Adverse Events

The investigator must monitor the condition of the patient throughout the trial from the time of obtaining informed consent until the last visit/trial-related contact.

The sources of adverse events cover:

- Investigations and examinations where the findings are assessed by the investigator to be clinically significant changes or abnormalities which are unanticipated in the setting of septic shock.
- The patient’s response to questions about his/her health (a standard non-leading question such as "How have you been feeling since your last visit?" is asked at each visit).
- Symptoms spontaneously reported by the patient.
- Other information relating to the patient’s health becoming known to the investigator (e.g. hospitalisation in the follow-up period).

8.2.2 Recording of Adverse Events

The investigator must record all adverse events in the adverse event log provided in each patient's eCRF with information about:

- Adverse event

- Date and time of onset (time can be omitted, if applicable)
- Intensity
- Causal relationship to the IMP
- Action taken to the IMP
- Other action taken
- Date and time of outcome (time can be omitted, if applicable)
- Outcome
- Seriousness

Each of the items in the adverse event log is described in detail in the following sections.

Adverse Event

Adverse events should be recorded as diagnoses, if available. If not, separate signs and symptoms should be recorded. One diagnosis/symptom should be entered per record.

If a patient suffers from the same adverse event more than once and the patient recovers in between the events, the adverse events should be recorded separately.

If an adverse event changes (decreases or increases) in intensity, a worst-case approach should be used when recording the event, i.e. the highest intensity and the longest duration of the event. Exception: if an adverse event with onset before the first administration of the IMP (i.e. a pre-treatment adverse event) changes in intensity after the administration of the IMP, this must be recorded as two separate events. The initial adverse event should be recorded with outcome “not yet recovered” and the date and time of outcome is when the intensity changed. The second adverse event should be recorded with date and time of onset when the intensity changed.

Pre-existing conditions not related to the patient’s current clinical setting of vasopressor-dependent septic shock are not adverse events, but become adverse events if worsening occurs after administration of the IMP during the trial. Pre-existing clinically significant conditions diagnosed or observed as a result of the screening procedures must be recorded as medical history.

Note the following: A procedure is not an adverse event; the reason for conducting the procedure is. However, a procedure may be captured along with the reason for conducting the procedure if the investigator finds it adds value to emphasise the procedure. Hospitalisation is not an adverse event; the reason for hospitalisation is. Death is not an adverse event, but the cause of death is (an exception is sudden death of unknown cause, which is an adverse event).

Overdoses and medication errors with or without clinical consequences are recorded as adverse events. The medication error must be specified. Any clinical consequence must be reported as “xxxx due to overdose/medication error”. In the absence of a clinical consequence this must specified e.g. “overdose with no clinical consequence”.

Date and Time of Onset

The date of onset is the date when the first sign(s) or symptom(s) were first noted. If the adverse event is an abnormal clinically significant laboratory test or outcome of an examination, the onset date is the date the sample was taken or the examination was performed. For pre-existing clinically significant conditions (diagnosed or observed as a result of the screening procedures) becoming worse after administration of the IMP, the date of onset is the date the worsening began. Time is to be recorded if relevant for the adverse event.

Intensity

The intensity of an adverse event must be classified using the following 3-point scale:

- Mild: Awareness of signs or symptoms, but no disruption of usual activity.
- Moderate: Event sufficient to affect usual activity (disturbing).
- Severe: Inability to work or perform usual activities (unacceptable).

Causal Relationship to IMP

The possibility of whether the IMP caused the adverse event must be classified as one of the following:

Reasonable possibility
There is evidence or argument to suggest a causal relationship between the IMP and the adverse event. The adverse event may occur as part of the pharmacological action of the IMP or may be unpredictable in its occurrence. Examples:

- Adverse events that are uncommon but are known to be strongly associated with exposure of the IMP.
- Adverse events that are not commonly associated with exposure of the IMP, but the event occurs in association with other factors strongly suggesting causation, such as a strong temporal association or the event recurs on rechallenge.

No reasonable possibility
There is no reasonable evidence or argument to suggest a causal relationship between the IMP and the adverse event. Examples:

- Known consequences of the underlying disease or condition under investigation.
- Adverse events common in the trial population, which are also anticipated to occur with some frequency during the course of the trial, regardless of exposure of the IMP.

Action Taken to IMP

The action taken to the IMP in response to an adverse event must be classified as one of the following:

- No change (medication schedule maintained or no action taken).

- Discontinued (medication schedule modified through permanent termination of prescribed regimen of medication).
- Paused (medication schedule was modified by temporarily terminating a prescribed regimen of medication).

Other Action Taken

Adverse events requiring therapy must be treated with recognised standards of medical care to protect the health and well-being of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.

If medication is administered to treat the adverse event, relevant medication will be entered in the medication forms and the serious adverse event form provided in each patient's eCRF.

Date and Time of Outcome

The date and time (if applicable) the patient recovered or died.

Outcome

The outcome of an adverse event must be classified as one of the following:

- Recovering (the event is improving).
- Recovered (the event has improved i.e. fully recovered or the condition has returned to the level observed at initiation of trial treatment).
- Recovered with sequelae (patient recuperated but retained pathological conditions resulting from the prior disease or injury e.g. resulted in persistent or significant disability / incapacity).
- Not recovered (the event has not improved).
- Fatal (termination of life as result of an adverse event).

8.3 Adverse Events of Special Interest

Some event types are considered especially important to record during this trial as they are considered a crucial part of both septic shock and the safety profile of the IMP. Event types that should always be reported as adverse events are:

- Episodes of atrial fibrillation and other cardiac arrhythmias that require treatment intervention, specifying the type of arrhythmia, treatment and/or intervention, severity and outcome.
- Stroke and other cerebrovascular events.
- Ischaemic events (myocardial ischaemia, peripheral ischaemia or mesenteric ischaemia).

8.4 Pregnancy

Known pregnancy is an exclusion criteria and women of child bearing potential will be tested for pregnancy and excluded if pregnant.

8.5 Serious Adverse Events

8.5.1 Serious Adverse Event Definition

An event is defined as being a serious adverse event if it:	**Guidance:**
Results in **death**	Any event resulting in a fatal outcome must be fully documented and reported, including deaths occurring within four weeks after the treatment ends and irrespective of the causal relationship to the IMP. The death of a patient enrolled in a trial is *per se* not an event, but an outcome (except in case of sudden death from unknown cause).
Is **life-threatening**	The term life-threatening refers to an adverse event in which the patient was at immediate risk of death at the time of the event. It does not refer to an event, which may have caused death if it were more severe.
Requires in-patient **hospitalisation** or prolongation of existing hospitalisation	The term hospitalisation means that the patient was admitted to hospital or that existing hospitalisation was extended as a result of an event. Hospitalisation describes a period of at least 24 hours. Over-night stay for observation, stay at emergency room or treatment on an out-patient basis do not constitute a hospitalisation. However, medical judgement must always be exercised and when in doubt the case should be considered serious (i.e. if case fulfils the criterion for a medically important event). Hospitalisations for administrative or social purposes do not constitute a serious adverse event. Hospital admissions and/or surgical operations planned before trial inclusion are not considered adverse events, if the illness or disease existed before the patient was enrolled in the trial, provided that the condition did not deteriorate during the trial.
Results in persistent or significant **disability/incapacity**	Disability/incapacity means a substantial disruption of a person's ability to conduct normal life functions. In doubt, the decision should be left to medical judgement by the investigator.
Is a **congenital anomaly/birth defect**	Congenital anomaly/birth defect observed in any offspring of the patient conceived during treatment with the IMP.
Is an **important medical event**	Important medical events are events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of important medical events include adverse events that suggest a significant hazard, contraindication or precaution, occurrence of malignancy or development of drug dependency or drug abuse. Medical and scientific judgement should be exercised in deciding whether events qualify as medically important. Important medical events include any suspected transmission of an infectious agent via a medicinal product. Any organism virus or infectious particle (e.g. prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a medicinal product.

8.5.2 Collection, Recording and Reporting of Serious Adverse Events

Serious Adverse Event Reporting by the Investigator

All serious adverse events must be reported **immediately** to Global Pharmacovigilance at Ferring as soon as it becomes known to the investigator and not later than within 24 hours of their knowledge of the occurrence of a serious adverse event.

The investigator is responsible for submitting the completed serious adverse event report form with the fullest possible details **within 3 calendar days** of his/her knowledge of the serious adverse event.

The serious adverse event report form is included in the eCRF system, and must be completed and submitted according to the instructions provided. In case the eCRF cannot be accessed and hence the serious adverse event report form cannot be filled in within the eCRF system, a paper serious adverse event report form should be used and sent to Global Pharmacovigilance at Ferring using the contact details below.

Global Pharmacovigilance, Ferring Pharmaceuticals A/S
E-mail: [redacted]
Fax: [redacted]

Completion of the demographics, adverse events, medical history, and concomitant medication are mandatory for initial reports and for follow-up reports if any relevant changes have been made since the initial report. Data entries must have been made in the eCRF for Ferring Global Pharmacovigilance to access the information.

Additional information relevant to the serious adverse event such as hospital records, results from investigations, e.g. laboratory parameters (that are not already uploaded in the eCRF), invasive procedures, scans and x-rays, and autopsy results can be faxed or scanned and e-mailed to Ferring Global Pharmacovigilance using the contact details in the section above. In any case this information must be supplied by the investigator upon request from Ferring. On any copies provided, details such as patient's name, address, and hospital identification number should be concealed and instead patient number should be provided.

The investigator will supply Ferring and the IEC/IRB with any additional requested information such as results of post-mortem examinations and hospital records.

Expedited Reporting by Ferring

Ferring will report all adverse events that are **serious, unexpected and with a reasonable possible causality to the IMP** as judged by either the investigator or Ferring to the relevant parties within the stipulated timelines.

Taking into consideration the patient population, fatal outcome of certain events occurring in the trial will be considered expected; a mortality rate of 20-25% has been assumed. Consequently the fatal outcome is not considered to be a reportable event, whereas the investigator must still report the events to Ferring as outlined above. If the cause of death is one of the below MedDRA terms or those medically judged to be similar, the event will not qualify for expedited reporting:

Circulatory collapse, distributive shock, endotoxic shock, septic shock, shock, toxic shock syndrome, acute respiratory failure, cerebral hypoperfusion, hypoperfusion, multi-organ failure.

The expectedness is assessed by Ferring according to the investigator's brochure for selepressin.

Serious adverse events will be considered reportable regardless of whether or not the IMP was used in accordance with the provisions in the protocol and investigator's brochure.

8.6 Follow-up of Adverse Events and Serious Adverse Events

8.6.1 Follow-up of Adverse Events with Onset during the Trial

During the trial, the investigator must follow-up on each adverse event until it is resolved or until the medical condition of the patient is stable.

After the patient's last visit, the investigator must follow-up on any adverse event that occurred during the trial and are classified as serious or considered to have a reasonable possible causality to the IMP with the outcome 'not recovered' until it is resolved or until the medical condition of the patient is stable. All such relevant follow-up information must be reported to Ferring. If the event is a chronic condition, the investigator and Ferring may agree that further follow-up is not required.

8.6.2 Collection of Serious Adverse Events with Onset after End of Trial

If an investigator becomes aware of a serious adverse event after the end of the trial, and he/she assesses the serious adverse event to have a reasonable possible causality to the IMP, the case will have to be reported to Ferring, regardless how long after the end of the trial this takes place.

9 STATISTICAL METHODS

The Global Biometrics department at Ferring will be responsible for the final statistical analyses. External statistical consultancies will be responsible for all interim analyses during the trial. All analyses will be detailed in a separate statistical analysis plan.

The Health Economics & Outcome Research department at Ferring will evaluate the cost-effectiveness of selepressin utilising relevant data recorded in this trial. Details of these analyses will be described in a separate health economic analytical plan.

The department of Experimental Medicine at Ferring will perform an analysis of pharmacokinetic parameters in a subset of patients. Details of this analysis will be described in a separate pharmacokinetic analysis plan.

9.1 Determination of Sample Size

At least 1800 evaluable patients combined for Part 1 and Part 2 are needed for the final analysis. The overall power of obtaining statistical significance based on combined evidence from Part 1 and Part 2 is 91% in situations where all four arms have a true underlying 1.5% lower mortality rate and a 1.5-day higher expected number of P&VFDs for survivors (corresponding to an overall treatment effect of 1.5 P&VFDs) as compared to placebo. If the effect sizes are 2% on mortality and 2 days for P&VFDs in survivors for all four arms (corresponding to an overall treatment effect of 2 P&VFDs) then the overall power is 98%. In this latter case the probability of engaging into Part 2 is ~99%. The four arms are described in Table 1.

9.2 Patient Disposition

A summary table will present, for each part of the trial and overall, the number of patients in the population sets: ‘Screened’, ‘Intention to treat’, Full analysis set’, ‘Per protocol’, ‘Safety’, ‘Completed trial’, ‘Withdrawals’, and ’IMP discontinuations’ with a breakdown of reasons/categories for and trial withdrawals and IMP discontinuations.

The patient disposition table will be broken down by each of the stratification variables [the need for mechanical ventilation (Yes/No), norepinephrine/noradrenaline requirement at baseline (< or ≥30 µg/min) and plasma/serum creatinine (< or ≥150 µmol/L)] and broken down chronologically displaying number of patients ‘completed’ and ‘withdrawn from trial’ at Day 30, Day 90, and Day 180.

The number of patients screened but not randomised/allocated to treatment will be presented with the reason(s) for screen failure in a data listing.

All major protocol deviations (including misrandomisation), based on the full analysis set (FAS), will be summarised for each part of the trial.

Furthermore, 1-Kaplan Meier (KM) plots, based on the intention-to-treat (ITT), will be presented for the time to trial withdrawals/IMP discontinuations (whichever comes first) differentiated by

reason for trial withdrawal/IMP discontinuation using cumulative incidence functions. Dropout rates between treatment groups will be evaluated by the log-rank test.

9.3 Protocol Deviations

Protocol deviations will be classified as 'minor' or 'major' by the Ferring clinical trial team on the basis of a blinded review of data before declaration of clean file and lock of database.

Major protocol deviations, such as significant non-compliance or other serious unforeseen violations deemed to invalidate the data and affect the conclusions of the trial, will lead to exclusion of data from the per protocol (PP) analysis set, while data will not be excluded because of minor protocol deviations. All major protocol deviations will be detailed and documented in the clean file document prior to database release. All protocol deviations (minor and major) will be listed in patient data listings.

9.4 Analysis Sets

9.4.1 Intention-to-Treat Analysis Dataset

The ITT analysis set comprises all randomised (as planned) patients.

9.4.2 Full Analysis Set

The FAS comprises data from all randomised (as planned) and dosed patients.

9.4.3 Per Protocol Dataset

Patients in the FAS will be excluded from the PP analysis set if they meet any major protocol deviations as defined in the statistical analysis plan. Data will be used up to the point of protocol deviation.

9.4.4 Safety Dataset

The safety analysis set comprises all treated patients and is analysed according to the actual treatment received.

9.5 Trial Population

9.5.1 Demographics and other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics (including vital signs) will be presented for the FAS population by treatment arm and total.

Categorical data will be summarised using numbers and percentages. The percentages are based on the total number of patients with a corresponding assessment. Continuous data will be presented, for example, using the number of patients, mean and standard deviation, median, interquartile range, minimum and maximum. All baseline characteristics will be listed.

9.5.2 Medical History and Prior/Concomitant Medication

Medical history will be summarised by treatment arm and total and presented in patient data listings.

Prior and concomitant medication will be summarised by treatment arm and total and presented in patient data listings.

9.6 Endpoint Assessments

9.6.1 General Considerations

All statistical tests will be performed using a two-sided test at a 5% significance level.

If the trial is stopped prematurely due to e.g. futility, the data will be analysed as planned in accordance with the statistical analysis plan.

The efficacy endpoints will be analysed for the FAS and the PP analysis set, with the FAS being considered as primary and the PP analyses as supportive.

Categorical data will be summarised using counts and percentages, while continuous data will be presented using the number of patients, mean, standard deviation, median, interquartile range, minimum and maximum.

All assessments will be listed in patient data listings.

9.6.2 Primary Endpoint

The primary endpoint of this trial is "vasopressor and mechanical ventilator-free days (P&VFDs) up to Day 30."

This composite endpoint is defined as the number of days (reported to one decimal place (0.0 to 30.0)) from start of treatment with the investigational medicinal product (IMP) [selepressin or placebo] to 30.0 days thereafter during which the patient is: 1) alive; 2) free of treatment with intravenous vasopressors; and 3) free of any invasive mechanical ventilation (see definition below).

Patient Death

By definition, any patient that dies within this 30-day period will be assigned zero P&VFDs, even if there is a period during which the patient is alive and free of both vasopressor treatment and mechanical ventilation.

Definition of "Free of Vasopressors"

Free of vasopressors means less than 60 minutes during any contiguous 24-hour period (regardless of calendar day). If a patient requires periods of vasopressors longer than 60 minutes in total during any 24-hour period, the intervening intervals during which they are free of vasopressors will not be included in the period free of vasopressors in the determination of the number of P&VFDs. Thus,

the period free of vasopressors begins at the end of the last use of vasopressors that was either: 1) longer than 60 minutes in duration; or 2) part of greater than 60 minutes of use within a contiguous 24-hour period.

Norepinephrine/noradrenaline, phenylephrine, dopamine, epinephrine/adrenaline, vasopressin, terlipressin, and IMP (i.e. selepressin and placebo) all constitute a vasopressor for the purpose of the primary analysis.

Vasopressor use due to anaesthesia or procedure-induced hypotension during and up to three hours after a surgery or procedure (including bedside) is exempt from this rule (i.e. such use of vasopressors would not affect the calculation of P&VFDs).

Definition of "Free of Mechanical Ventilation"

Mechanical ventilation is defined as use of endotracheal or tracheostomy tube assisted ventilation (>5 cm H_2O continuous positive airway pressure and >5 cm H_2O of pressure support from the ventilator in tracheostomy patients). End of mechanical ventilation is defined as: 1) extubation of intubated patients or 2) ≤5 cm H_2O continuous positive airway pressure and ≤5 cm H_2O of pressure support from the ventilator in tracheostomy patients. If non-invasive ventilation by mask or bag (>5 cm H_2O of pressure support) is deployed to avoid (re)intubation, it also counts as mechanical ventilation. However, all other uses of non-invasive ventilation such as chronic night-time use of positive airway pressure for COPD or sleep apnea does not count as mechanical ventilation (regardless of pressure). Free of mechanical ventilation means less than 60 minutes during any contiguous 24-hour period (regardless of calendar day). If a patient requires mechanical ventilation for periods longer than 60 minutes in total during any 24-hour period, the intervening intervals during which they are not receiving mechanical ventilation will not be included in the period free of mechanical ventilation in the determination of the number of P&VFDs. Thus, the period free of mechanical ventilation begins at the end of the last use of mechanical ventilation that was either: 1) longer than 60 minutes in duration; or 2) part of greater than 60 minutes of use within a contiguous 24-hour period.

The use of mechanical ventilation associated with anaesthesia or procedural sedation during and up to three hours after a surgery or procedure (including bedside) is exempt from this rule (i.e. such use of mechanical ventilation would not affect the calculation of P&VFDs).

It is important to note that the determination of freedom from vasopressors and freedom from mechanical ventilation are made separately; in other words, periods of vasopressor use and mechanical ventilation are not combined when determining whether 60 minutes of use has occurred within a 24-hour period.

Missing data during the time of hospitalisation will be imputed using a worst case approach taking into account previous and subsequent starting and stopping times of vasopressor administration and mechanical ventilation. If only the stop date but not time is given, the imputed time will be midnight of that date, unless a subsequent starting time was recorded prior to midnight in which

case the imputed time would be the start time of the subsequent record. If neither stop date nor time is given, the imputed stop time will be the start date and time of the subsequent recording. Likewise, missing start dates and times would be imputed as worst case scenarios, i.e. is the patient found to be on mechanical ventilation with a date but no time for intubation, the imputed start time would be recorded as 00:01 of that day or the stop date of a preceding recording on that same date, whichever occurs last. If both start date and time is missing, the imputed start time would be the date and time of the preceding stop time recorded. In case of data being completely missing from a certain time point and onwards, the "last status carried forward" imputation will be applied. If a patient was last seen on either ventilator or vasopressors, it is assumed that the patient remained so, and is imputed to a value of 0 (zero) P&VFDs. If the patient was last seen off ventilator and vasopressors, it is also assumed that the patient remained so in the remaining 30-day period. If the patient was last seen (alive) on e.g. day 10 and at that point had been off both ventilator and vasopressors for three days, a value of 23 P&VFDs is imputed.

The primary endpoint, P&VFDs, will be analysed using a van Elteren test, stratified by need for ventilation (Yes/No), time from onset of shock (onset of any vasopressor) to start of IMP treatment (< or ≥6 hours), and norepinephrine/noradrenaline requirement at baseline (< or ≥30 µg/min).

The primary analysis will compare all patients on all selepressin arms from both parts of the trial (pooled together and treated as a single arm) to all patients on the placebo arm from both parts of the trial. The primary analysis will be a test of superiority using a two-sided 5% significance level test. This test, within the trial, controls the type 1 error at a two-sided 5% level. Further details are provided in the statistical analysis plan.

Treatment effects will be estimated assuming a negative binomial distribution (to allow for possible overdispersion in a Poisson distribution) for the quantity (30 minus P&VFDs) for survivors, and a binomial distribution to model the probability of surviving. Both models adjusted for need for ventilation (Yes/No), time from onset of shock to start of IMP treatment (< or ≥6 hours), and norepinephrine/noradrenaline requirement at baseline (< or ≥30 µg/min). Further details are provided in the statistical analysis plan.

Furthermore, P&VFDs will be tabulated by treatment arm (including pooled active treatment arms), and presented graphically by histograms and cumulative distributions functions.

The success (statistical/clinical significance) of the trial will be based upon the comparison of the analysis above (all patients on all selepressin dosing regimens from both parts of the trial [pooled together and treated as a single arm] compared to all patients on the placebo arm from both parts of the trial).

9.6.2.1 Sensitivity Analyses of the Primary Endpoint

As the adaptations of the trial provide a conservative estimate of the p-value, sensitivity p-values will be provided using post-simulation bootstrap calculations.

In order to check for consistency, the primary endpoint treatment differences will, as a minimum, be estimated and presented by forest plots for the following subgroups:

- Region
- Age
- Gender
- Race/ethnicity

Furthermore, the primary endpoint will be stratified by severity of the patients, with risk of dying as indicator of severity (see Figure 3). Mortality (the risk of dying) will be analysed by a logistic regression model, with relevant baseline characteristics as covariates (e.g. the individual SOFA scores and age). The model used to generate the predicted risk (for all patients) will be based on patients in the placebo arm only, as the risk of dying should reflect the severity in the absence of selepressin. Stratified by the risk of dying (intervals of 20% if suitable, based on the mortality rates in the covariate categories in the model), the treatment effect of the primary endpoint will be presented graphically, in order to visually inspect whether the average treatment effect is distributed evenly across the severity of patients.

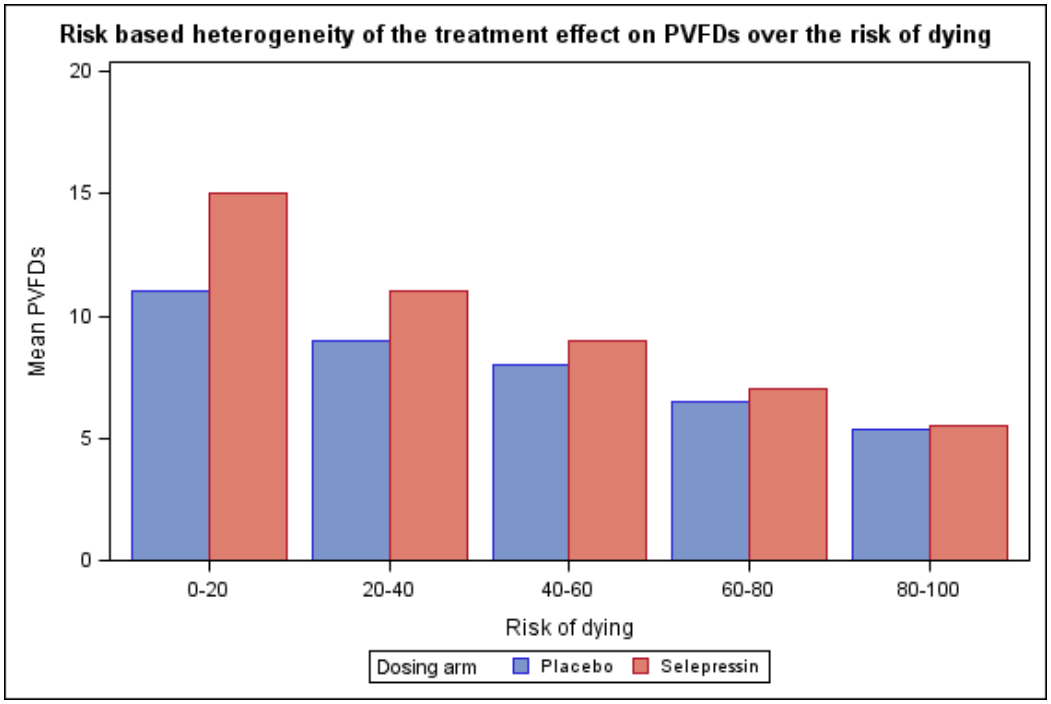


Figure 3 Risk-based Heterogeneity of the Treatment Effect on P&VFDs over the Risk of Dying (an example)

The impact and robustness of the imputation of missing data will be checked by analysing data in the following ways

- excluding all patients with missing/imputed data
- imputing the 30-day P&VFD status for patients lost to follow up or otherwise withdrawn from trial using the observed ratio of P&VFDs at time of lost to follow up or time of withdrawal, to the same proportion for a 30-day status

For this analysis the 30-day P&VFD status for patients lost to follow up or otherwise withdrawn from trial will be imputed so that the 30-day ratio of P&VFDs is equal to the ratio of P&VFDs at time of lost to follow up or time of withdrawal. E.g. a patient being lost to follow up at Day 15 with 4 P&VFDs (a ratio of 4/15 P&VFDs per days observed) will be imputed to 8 P&VFDs at Day 30 (equivalent ratio 8/30 = 4/15). Patients having zero P&VFDs at time of lost to follow up will be imputed to a value of zero P&VFDs.

- tipping point analysis

The tipping point analysis will compare all possible combinations of 'best case' and 'worst case' scenarios between placebo and selepressin for patients lost to follow up or otherwise withdrawn from trial. Best case being an imputation assuming the remaining days off ventilator and vasopressors, and worst case being an imputation of zero P&VFDs. N_P and N_S will be the number of patients in the placebo and selepressin arms with missing data. The tipping point analysis will compare all combinations (from 0 to N_P) of X patients on placebo imputed best case and $N_P - X$ imputed worst case, to Y patients on selepressin imputed best case and $N_S - Y$ imputed worst case. In other words, all $N_P + 1$ times $N_S + 1$ combinations will be analysed for the primary endpoint. Since the 'best case' is not the same for all patients (depending on when they were last seen off both ventilator and vasopressors), there are multiple outcomes within each combination. For each combination, the average p-value of the multiple outcomes will be plotted in the tipping point analysis.

Below is an example of a tipping point analysis of 25 placebo versus 40 selepressin patients with imputed values. The x- and y-axis displays the number of patients with the 'best case' imputed. In the example in Figure 4, the red area displays the non-significant p-values, indicating that one would have to impute almost all placebo patients to a 'best case' and almost all selepressin to a 'worst case' in order to get non-significant p-values, and hence 'proving' the robustness of the imputation method.

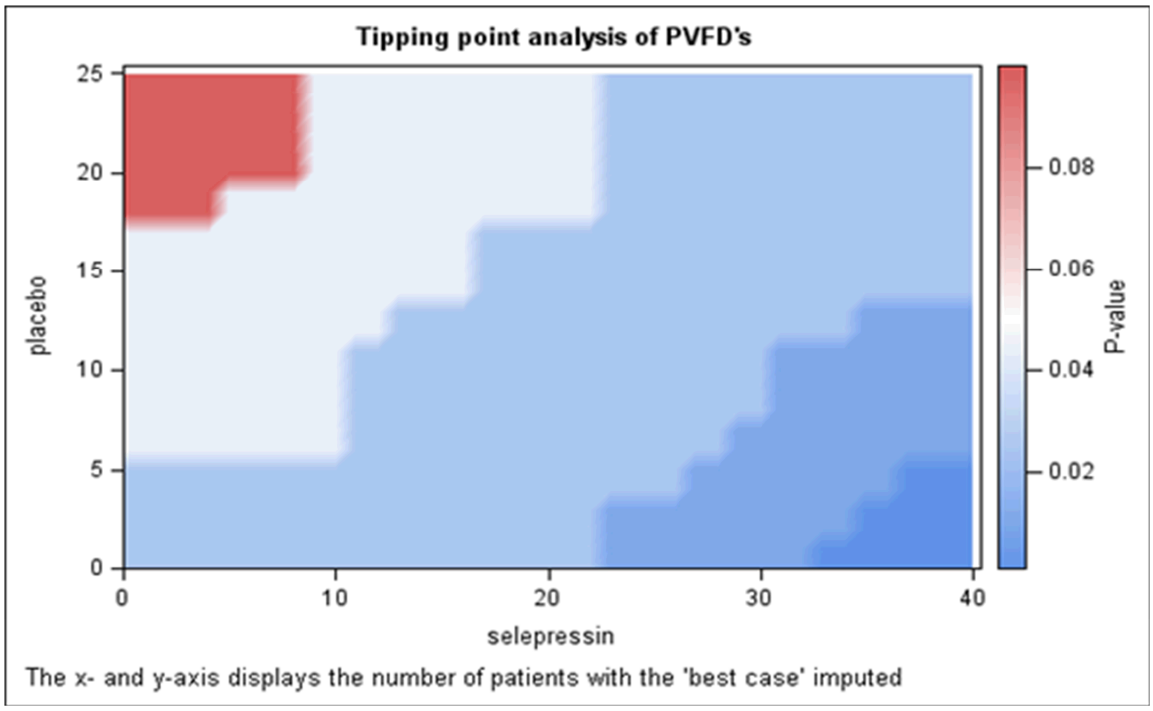


Figure 4 Tipping Point Analysis of P&VFDs (an example)

Also, to make sure that the use of vasopressor in each group is not simply being replaced by an increased use of inotropic agents, there will be a sensitivity analysis of the primary endpoint in which the use of inotropic agents will count as vasopressor use.

9.6.2.2 Additional Analyses

The primary analysis will be repeated for:

- The selected dose only, i.e. comparing all patients on the selected dose (from Part 1) from both parts of the trial (pooled), to all patients on the placebo arm from both parts of the trial.
- Data from Part 2 only, i.e. comparing the selected dose to placebo on data from Part 2 only.

9.6.3 Secondary Endpoints

For the purpose of a possible label inclusion, the Hochberg procedure for adjustment on multiplicity will be implemented to selected key secondary endpoints. Only if the primary efficacy analysis leads to a statistically significant result at the (one-sided) 2.5% level, then the Hochberg procedure, which is described below, is applied to the selected key secondary analyses. If the primary efficacy analysis does not result in statistical significance at the (one-sided) 2.5% level, then statistical significance (for the purpose of a possible label inclusion only) will not be declared for any of the key secondary analyses, regardless of their p-values.

The selected key secondary endpoints aimed at further demonstrating treatment effect are:

- All-cause mortality (defined as the fraction of patients that have died, regardless of cause) at Day 90
- RRT-free days up to Day 30 (excluding patients on RRT for chronic renal failure at time of randomisation)
- ICU-free days up to Day 30

In this application of the Hochberg procedure there are three hypothesis tests of superiority for each of the selected secondary endpoints. The target alpha level is (one-sided) 2.5%. The Hochberg procedure is as follows:

- Order the p-values from the smallest to the largest value, $p(1) < p(2) < p(3)$, with corresponding null hypothesis $H_{(1)}$, $H_{(2)}$, and $H_{(3)}$.
- Start with the highest p-value. If $p(3) < 2.5\%$ (one-sided), then stop and declare all three comparisons significant at the 2.5% (one-sided) level (i.e. reject $H_{(1)}$, $H_{(2)}$, and $H_{(3)}$). Otherwise, accept $H_{(3)}$ for the endpoint related to p(3), and go to p(2) the second highest p-value.
- If $p(2) < 2.5/2 = 1.25\%$ (one-sided), then stop and declare significance for $H_{(1)}$ and $H_{(2)}$. Otherwise, accept $H_{(2)}$, for the endpoint related to p(2), and go to p(1) the lowest p-value.
- If $p(1) < 2.5/3 = 0.833\%$ (one-sided), then stop and declare significance for $H_{(1)}$. Otherwise, accept $H_{(1)}$, for the endpoint related to p(1).

Regardless of the statistical significance declared according to the Hochberg procedure, all analyses will be included and presented in the statistical report.

As for the primary analysis, the primary comparison (which determines the success, i.e. statistical and clinical significance) for the secondary efficacy endpoints is between all patients on all selepressin arms from both parts of the trial (pooled together and treated as a single arm) and all patients on the placebo arm from both parts of the trial.

As an additional analysis, all secondary efficacy analyses will, as for the primary, be repeated for:

- The selected dose only, i.e. comparing all patients on the selected dose (from Part 1) from both parts of the trial (pooled), to all patients on the placebo arm from both parts of the trial.
- Data from Part 2 only, i.e. comparing the selected dose to placebo on data from Part 2 only.

All free-days endpoints will be reported to one decimal place.

The following secondary endpoints will be defined and analysed in a similar manner as the primary endpoint:

- ***Vasopressor-free Days up to Day 30***
- ***Mechanical ventilator-free Days up to Day 30***

- ***RRT-free Days up to Day 30 (excluding patients on RRT for chronic renal failure at time of randomisation)***
- ***ICU-free Days up to Day 30***

Incidence of RRT up to Day 30 (excluding patients on RRT for chronic renal failure at time of randomisation) is defined as any form of renal replacement therapy defined as continuous renal replacement therapy, intermittent haemodialysis, or peritoneal dialysis. In order to ensure that any reduction in incidence of RRT is not caused by an increase in mortality, all patients dying within the 30-day period will be counted as on RRT. For patients withdrawn prior to Day 30, incidence of RRT will be based on the data available up until the time of withdrawal.

Incidence of RRT will be analysed by a logistic regression model with time from onset of shock to start of treatment, baseline creatinine and norepinephrine/noradrenaline requirement at baseline (µg/kg/min), as covariates, and treatment, and need for ventilation as factors. The 95% confidence interval for the difference in proportions between treatment groups will be constructed using the delta method. Patients already on RRT at time of inclusion will be excluded from the analysis of incidence of RRT.

Non-inferiority will be claimed if the upper limit of the two-sided 95% CI of the adjusted difference in proportions is less than 20% of the estimated incidence of RRT in the placebo group. Superiority can be claimed if the upper limit is less than 0.

I.e., let $\widehat{p_S}$ and $\widehat{p_P}$ be the estimated incidences of RRT in the combined selepressin groups and the placebo group respectively. Non-inferiority will then be claimed if

$$\widehat{p_S} - \widehat{p_P} + 1.96 * \sqrt{var(\widehat{p_S} - \widehat{p_P})} < 0.2 * \widehat{p_P}$$

and superiority will be claimed if

$$\widehat{p_S} - \widehat{p_P} + 1.96 * \sqrt{var(\widehat{p_S} - \widehat{p_P})} < 0$$

Furthermore, incidence of RRT will be tabulated by treatment arm (including pooled active treatment arms).

A subgroup analysis will be performed on patients without acute RRT at baseline.

Duration of septic shock up to Day 30. Shock is defined as the cumulative periods (>1 hour) from start of IMP until Day 30, on IMP or vasopressors. Vasopressor use due to anaesthesia / procedure-induced hypotension during - and up to three hours after - surgery / procedure (including bedside) is exempt from this rule. For patients withdrawn (in the survivors analysis) or dying (in the non-survivors analysis) while still in septic shock, the duration will be based on the data available up until the time of withdrawal or death.

Duration of septic shock will be analysed separately for survivors, non-survivors (within the first 30 days) and overall, comparing treatment arms by an analysis of covariance (ANCOVA) model with time from onset of shock to start of treatment and norepinephrine/noradrenaline requirement at baseline (µg/kg/min) as covariates, and treatment and need for ventilation (Yes/No) as factors. The estimated treatment difference (to placebo) with a 95% confidence interval will be presented.

Some patients will get out of shock prior to Day 30 (and stay alive until Day 30), some will get out of shock and die later on (prior to Day 30), others will die while still in shock (prior to Day 30), and the remaining few will not get out of shock prior to Day 30. This means that if mortality rates vary between treatment arms, the results of the analysis for the overall population will be influenced by the skewed mortality rates. Hence, for the overall population, the distribution of duration of shock (time to out of shock), will be presented graphically as competing risks between 'time to out of shock' and 'dying while in shock'. Further, a KM (sub)-graph on 'time to death' will be presented for those getting out of shock (for which some will die later on, prior to Day 30). This is done in order to elucidate any skewness in mortality rates, influencing the results of the analysis. The duration of septic shock will also be tabulated by treatment arm (including pooled active treatment arms).

The following secondary endpoints will be defined and analysed in a similar manner as for duration of septic shock:

- ***Duration of mechanical ventilation up to Day 30***
- ***Duration of RRT up to Day 90 (excluding patients on RRT for chronic renal failure at time of randomisation)***
- ***ICU length of stay up to Day 30***

Daily overall (modified) and individual organ scores of the SOFA will be compared between treatment arms up until Day 7 using a repeated measures ANCOVA model with baseline SOFA score as covariate, treatment, time and treatment by time interaction as factors, and patient as the experimental unit. The estimated treatment difference (to placebo) with a 95% confidence interval will be presented.

Last observation carried forward (LOCF) will be used for missing SOFA scores on Days 2-7. No LOCF for Day 1 (as previous value is baseline). Patients dying will be imputed with a worst possible outcome, i.e. a value of 4 for each individual SOFA score.

Daily overall (modified) and individual SOFA scores will be tabulated by treatment arm (including pooled active treatment arms).

Incidence of new organ dysfunction and new organ failure. New organ failure is defined as an increase (i.e. worsening) in any of the individual SOFA scores from (0, 1, 2) at baseline to (3, 4) post baseline up until the end of the period (Days 7 or 30) (if the SOFA scores goes from [0, 1, 2] to [3, 4] and back to [0, 1, 2] again within the period, that will still count as a new organ failure). If a

patient dies within the period, he/she is considered to fail on all organs, and the number of new organ failures will be all organs except those already failed at baseline. Patients discontinued within the period will be evaluated based on the data available at time of discontinuation.

Incidence of new organ dysfunction is defined as an increase ≥1 from baseline to post baseline up until the end of the period (e.g. going from 1 to 2) in any of the individual SOFA scores. Patients with an individual SOFA score of 4 at baseline can per default not have a new organ dysfunction. If a patient dies within the period, he/she is considered to have dysfunction on all organs, and the number of new organ dysfunctions will be all organs except those already having a score of 4 at baseline. Patients withdrawn within the period will be evaluated based on the data available at time of withdrawal.

Incidence of at least one new organ failure will be analysed for any new organ failure (across all organ systems) and by individual organ systems, and compared between treatment arms using a logistic regression model with age, modified SOFA score, and norepinephrine/noradrenaline requirement at baseline (µg/kg/min) as covariates and gender and treatment arm as factors, presenting odds ratios with 95% confidence intervals.

Incidence of at least one new organ dysfunction will be analysed for any new organ dysfunction (across all organ systems) and by individual organ systems, and will be analysed as above for new organ failures.

The number of new organ dysfunctions and new organ failures will be compared between treatment arms using a negative binominal model with age, modified SOFA score, and norepinephrine/ noradrenaline requirement at baseline (µg/kg/min) as covariates, and gender and treatment as factors. The estimated treatment difference (to placebo) with a 95% confidence interval will be presented. The 95% confidence interval for the difference in proportions between treatment groups will be constructed using the delta method.

Incidence of any new organ dysfunction and any new organ failure and the number of new organ dysfunctions and new organ failures will be tabulated by treatment arm (including pooled active treatment arms).

All-cause mortality is defined as the fraction of patients that have died, regardless of cause, by the end of Day 30, Day 90, and Day 180 and will be analysed and compared between treatment arms using a logistic regression model with the individual SOFA scores and age as covariates and treatment arm as factor. The 95% confidence interval for the difference in proportions between treatment groups will be constructed using the delta method as for incidence of RRT. There will be no imputations for mortality.

Non-inferiority will be claimed if the upper limit of the two-sided 95% CI of the adjusted difference in proportions is less than 30% of the estimated incidence of mortality in the placebo group. Superiority can be claimed if the upper limit is less than 0.

Assuming an observed 30-day mortality rate of 20-25% in the placebo group, a non-inferiority limit of 30% corresponds to a maximum observed mortality rate of 2-3% in the combined selepressin groups in order for selepressin to be non-inferior to placebo.

Furthermore, mortality will be tabulated by treatment arm (including pooled active treatment arms), and the time to death presented graphically by a Kaplan-Meier plot.

EQ-5D-5L will be analysed by the index value, the overall quality-adjusted life years (QALY) at Day 30 and 180, and the VAS score. The QALY scores will NOT be adjusted to e.g. a half yearly time scale at Day 180. As the QALY is not defined for patients with all remaining values missing, and hence also not defined for those who die, the analyses will automatically only be analysed for those surviving up until Day 30 and Day 180, respectively.

For patients with missing baseline index value, the QALY score will also be set to missing. For robustness, a sensitivity analyses will be performed, imputing the missing baseline scores with the overall mean of the baseline health index. Baseline is the timing prior to acute admission.

The QALY at Day 30 and Day 180 will be compared between treatment arms using an ANCOVA model with baseline health index as covariate, and treatment as factor. Estimated treatment differences (to placebo) along with a 95% confidence interval will be presented.

The index value and VAS scores will be analysed separately for survivors and non-survivors at Day 180 (since all non-survivors will have non-random missing values, and hence would artificially inflate the mean estimates if survivors and non-survivors were analysed together) and will be compared between treatment arms using a repeated measures ANCOVA model with baseline health index/VAS score as covariate, treatment, time and treatment by time interaction as factors, and subject as the experimental unit. Estimated treatment differences (to placebo) along with a 95% confidence interval will be presented for Day 30, Day 60, Day 90, and Day 180. There will be no imputations for missing values.

The QALY, index value, and VAS scores will be tabulated by treatment arm (including pooled active treatment arms), and the index value and VAS scores will be presented graphically.

Daily and cumulative fluid balance (for 7 days or until ICU discharge). Fluid overload is defined as fluid balance as a percentage of baseline weight (e.g. if a patient weighs 90 kg at baseline and has a fluid balance of 9 litres, fluid overload is then 100% * 9 litres / 90 kg = 10%.

Fluid balance and cumulative fluid balance will be presented both unadjusted and adjusted for weight.

Daily and cumulative fluid balance as well as daily and cumulative fluid overload will all be compared between treatment arms using a repeated measures ANCOVA model with baseline (baseline fluid balance or baseline fluid overload) as covariate, treatment, time and treatment by

time interaction as factors, and patient as the experimental unit. Estimated treatment differences (to placebo) along with a 95% confidence interval will be presented.

The absolute values and change from baseline will be tabulated by treatment arm (including pooled active treatment arms), and presented graphically.

All analyses will be presented for 'all patients' and for 'patients in ICU throughout Day 0-7'.

Daily and cumulative Urine Output (for 7 days or until ICU discharge) will be analysed as for fluid balance.

9.6.4 Other Efficacy Endpoints

Other assessments include:

- Hospital-free Days up to Day 90

Will be defined and analysed in a similar manner as for the primary endpoint.

- Hospital length of stay up to Day 90

Will be defined and analysed in a similar manner as for duration of septic shock.

- Norepinephrine/noradrenaline and other vasopressor doses

The dose of norepinephrine/noradrenaline administered (adjusted for baseline weight) will be compared between treatment arms using a repeated measures ANCOVA model with baseline dose of norepinephrine/noradrenaline as covariate, treatment, time and treatment by time interaction as factors, and patient as the experimental unit. Estimated treatment differences (to placebo) along with a 95% confidence interval will be presented. If a patient has missing values and the patient is still in the trial (not dead or withdrawn) it will be assumed that the specific vasopressor was not given and a value of zero will be imputed, unless there is an interval in the timing log covering the exact time point (8 AM and 8 PM is the assumed time point for missing morning and evening collection time points). In that case LOCF will be used, but only within the time interval.

The mean dose administered will be tabulated by treatment arm (including pooled active treatment arms), and presented graphically.

The same analysis (adjusted for baseline dose of norepinephrine/noradrenaline) will be performed for the following endpoints:

- Catecholamines (defined as the sum of doses of norepinephrine/noradrenaline, epinephrine/adrenaline, dopamine, and phenylephrine)

- Catecholamines excluding norepinephrine/noradrenaline

- Vasopressin

For the sum of catecholamine doses we define 100 µg dopamine, 1 µg epinephrine, and 2.2 µg phenylephrine all equivalent to 1 µg norepinephrine.

Also, the number of patients receiving terlipressin will be summarised.

- Patient residence at Day 30, Day 60, Day 90, and Day 180
- MAP
- Arterial blood gases and acid/base status (PaO_2, $PaCO_2$, SaO_2, pH, bicarbonate, base excess) and lactate levels
- $ScvO_2$
- PaO_2/FiO_2 (in a subset of patients)
- EVLW and PPI (in a subset of patients)
- Cardiac output (in a subset of patients)
- Cytokines, angiopoietin-1 and -2 levels (in a subset of patients)

These assessments will be presented by descriptive statistics, i.e. the number of patients with data, mean (standard deviation), median, interquartile range, minimum, and maximum values, will be presented for observed values and change from baseline at each time-point. Baseline value will be the value obtained at the last assessment prior to the infusion start of the IMP.

- Creatinine clearance

Creatinine clearance will be analysed as for fluid balance with baseline creatinine clearance as a covariate, treatment, time and treatment by time interaction as factors, and patient as the experimental unit.

9.7 Extent of Exposure and Treatment Compliance

The total amount (adjusted by weight [µg/kg]) of selepressin administered and the number of (decimal) days treated with selepressin will be summarised by (active) treatment arm and total (active treatment arms).

Furthermore, the mean cumulative amount administered and the mean infusion rate will be tabulated by treatment arm and presented graphically (also by treatment arm and total).

9.8 Safety

9.8.1 General Considerations

Safety parameters will be evaluated for the safety analysis data set. All safety summaries will be tabulated by treatment arm (including pooled active treatment arms).

9.8.2 Adverse Events

Adverse events will be classified according to the medical dictionary for regulatory activities (MedDRA). The MedDRA version will be documented.

A pre-treatment adverse event is any adverse event occurring after informed consent and before administration of the IMP.

A treatment-emergent adverse event is any adverse event occurring after the administration of the IMP and within the time of residual drug effect (i.e. 12 hours), or a pre-treatment adverse event or pre-existing medical condition that worsens in intensity after start of IMP and within the time of residual drug effect. The time of residual drug effect is the estimated time after the end of the administration of the IMP, where the effect of the product is still considered to be present based on pharmacokinetic, pharmacodynamic, or other substance characteristics. A generally accepted time for residual drug effect is 5 half-lives. The terminal half-life of selepressin is expected to be not more than 1.8 hours, and hence, a treatment-emergent adverse event is defined as any adverse event occurring after the start of IMP infusion and within 12 hours after the IMP infusion is stopped.

A post-treatment adverse event is any adverse event occurring after the residual drug effect period.

Missing values will be treated as missing, except for causality, intensity, seriousness, and outcome of adverse events. A "worst case" approach will be used: if causality is missing, the adverse event will be regarded as related to the IMP; if the intensity of an adverse event is missing, the adverse event will be regarded as severe; if seriousness is missing the adverse event will be regarded as serious; if start date is missing or incomplete, worst case will be assumed and the adverse event will be regarded as treatment-emergent (only if the incomplete start date is not compromised). If start date is completely missing, start date will be set as same day as start of treatment. If start date is incomplete, the date closest to start of treatment will be assumed, without compromising the incomplete data available on the start date; if outcome is missing and no date of outcome is present the outcome is regarded as 'not recovered'.

Adverse event overview summary tables will be prepared for treatment-emergent AEs and all AEs (treatment-emergent and non treatment-emergent) including the number of patients reporting an adverse event, the percentage of patients with an adverse event, and the number of events reported, for the following categories:

- Adverse events
- Deaths
- Serious adverse events
- Adverse events leading to discontinuation of IMP
- Severe and life-threatening adverse events
- Adverse drug reactions

Adverse events will be summarised in a table by SOC (sorted alphabetically) and PT (sorted in decreasing frequency of occurrence) using MedDRA. The table will display the total number of patients reporting an adverse event, the percentage of patients with an adverse event, and the number of events reported.

For both treatment-emergent AEs and all AEs (treatment-emergent and non treatment-emergent) during the treatment period, summary tables will be prepared for:

- All adverse events
- Adverse events with an incidence ≥5% of patients in any treatment arm
- Non-serious adverse events with an incidence ≥5% of patients in any treatment arm
- Critical adverse events, details are provided in the statistical analysis plan
- Adverse events by causality (related/unrelated)
- Adverse events leading to death
- Adverse events by intensity
- Serious adverse events
- Adverse events leading to discontinuation of IMP (related/unrelated)

Supporting data listings will be provided for:

- All adverse events sorted by trial site and patient number
- All adverse events sorted by MedDRA PT
- Serious adverse events
- Adverse events leading to death
- Adverse events leading to discontinuation of IMP (related/unrelated)
- Post-treatment adverse events

9.8.3 Safety Laboratory Variables

Safety laboratory variables will be grouped under 'Clinical Chemistry', 'Haematology', and 'Coagulation'.

Baseline for all safety laboratory variables will be the values obtained at the last assessment prior to the infusion start of the IMP. End of treatment period will include the last post-baseline observation during the trial up until Day 30.

Mean change and mean percentage change from baseline at end of treatment period will be presented for each laboratory variable. In addition, descriptive statistics, i.e. the number of patients with data, mean (standard deviation), median, interquartile range, minimum, and maximum values, will be presented for observed values and change from baseline at each time-point for each laboratory variable.

Also, summary tables will be presented, displaying by time and laboratory parameter, the number of patients with a clinically significant result which is unanticipated in the setting of septic shock.

Furthermore, a summary table will be prepared for selected laboratory variables that display the number and percentage of patients in each treatment arm with X% increments (increase or

decrease) from baseline at each time-point. The selected laboratory variables and categories are detailed in the statistical analysis plan.

9.8.4 Vital Signs and Central Venous Pressure

Baseline for all vital signs variables and CVP will be the values obtained at the last assessment prior to the IMP infusion start. End of treatment period will include the last post-baseline observation during the trial up until Day 30.

Mean change and mean percentage change from baseline at end of treatment period will be presented for each variable. In addition, descriptive statistics, i.e. the number of patients with data, mean (standard deviation), median, interquartile range, minimum, and maximum values, will be presented for observed values and change from baseline at each time-point for each variable.

Also, summary tables will be presented, displaying by time and vital signs parameter, the number of patients with a clinically significant result which is unanticipated in the setting of septic shock.

Furthermore, a summary table will be prepared for each variable that display the number and percentage of patients in each treatment arm with X% increments (increase or decrease) from baseline at each time-point and end of treatment period. The variables and categories are detailed in the statistical analysis plan.

9.8.5 Episodes of Hypotension

Descriptive statistics of number of patients with episodes of hypotension and the total length of periods with hypotension will be summarised by treatment arm.

The total length of periods with hypotension will be summarised for both all patients, and patients having one or more episodes of hypotension.

9.9 Interim Analyses

There will be no interim analyses with the potential to stop the trial early for treatment efficacy. However, once the “burn-in” period in Part 1 is completed (first 200 treated patients), interim analyses will be conducted regularly to improve the efficiency of dose selection and to allow early termination of the part or the trial for futility or for successful dose selection. The following steps will be considered at each interim analysis:

- When 200 patients are treated, the allocation probabilities for the active treatment arms are changed using response-adaptive randomisation (with placebo still 1/3). For the two-thirds of patients assigned to the active arms, the probability that a given active arm is assigned to a patient is proportional to the probability that that arm is the arm with the largest expected number of P&VFD.
- Potentially stopping the trial for futility during Part 1. This occurs if no active arm has better than a 5% predictive probability of a significant result in Part 2 if it were to start

immediately. This decision can occur at any interim during Part 1 after 200 evaluable patients.

- Potentially ending Part 1 and selecting an active treatment arm to continue to Part 2. This decision can occur at any interim analysis between 300 evaluable and 800 treated patients, and it occurs if some arm has a predictive probability of a successful trial of at least 90% before 800 treated patients, and the threshold drops to 25% for the final Part 1 interim analysis at 800 treated patients. The selected arm is the arm with the largest posterior predictive probability of trial success. This will generally be the best-performing active arm, but if multiple arms are performing equally well, it will be the arm with the lowest dosing level. If Part 1 ends after *N* patients, then Part 2 will consist of up to 1800 - *N* evaluable patients.
- If the trial is not stopped for futility or proceeding to Part 2 and active treatment Arm 4 has not yet been approved for assignment of patients, the decision can be made to open up Arm 4. Arm 4 is only opened between 200 evaluable and 600 treated patients and if there is at least a 50% probability that Arm 3 has a higher expected P&VFD than Arm 2 and if data from the lower dosing levels do not suggest any significant safety signals.
- If Part 1 reaches its maximum of 800 treated patients and no arm has a predictive probability of Part 2 success of more than 25%, the trial stops with an inconclusive result and will be interpreted as a standalone Phase 2b trial.

During Part 2, interim analyses will be conducted regularly (until 1600 patients have been treated) to allow early termination of the trial for futility. This occurs if the predictive probability of an overall significant result is less than 5%. In addition, if the predictive probability of observing a more than 2% higher mortality in the active arms compared to placebo is greater than 90% then the trial will stop for futility.

10 DATA HANDLING

10.1 Source Data and Source Documents

Source Data – ICH Definition

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents - ICH Definition

Source documents are defined as original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

Trial-specific Source Data Requirements – Ferring

The investigators must maintain patient records. For each randomised patient, the investigators will indicate in the hospital/medical source records that the patient participates in this trial and the date of obtaining the informed consent. The records will include data on the condition of the patient at the time the patient is enrolled in the trial in order to document (and enable verification of) eligibility. Signed and dated informed consent forms will be stored and archived in accordance with local requirements.

The following information, as a minimum, has to be recorded in the hospital/medical source records for each patient:

- Documentation of informed consent obtained
- Trial identification
- Screening/patient (randomisation) number
- Patient's name
- Demographic data including date of birth, race, and ethnic origin
- Diagnosis, septic shock characteristics
- Relevant medical history
- Relevant concomitant medications/procedures
- Body weight and height
- Eligibility for participation in the trial (documenting all inclusion/exclusion/eligibility criteria)

- Details of the administration of IMP
- Details of the administration of norepinephrine/noradrenaline and other vasopressors
- Details of the MAP during the IMP infusion
- Details of mechanical ventilation (including spontaneous breathing trials) and RRT
- Functional/survival status of the patient throughout the trial
- ED/ICU/hospital admission and discharge dates and times
- Details and results of all other examinations and tests performed
- Date of each visit/contact
- Details of adverse events
- Reason for discontinuation/withdrawal, if applicable

Information included in the patient's hospital records may be subject to local regulations. If there is a discrepancy between local requirements and the trial protocol, local regulations should be followed. The identification of source data for each variable may then be described in a separate document.

Documents collected during the trial (e.g. health-related quality of life questionnaires, laboratory reports, print-outs of MAP and ECG) should be stored and archived together with the patient's hospital/medical records or in the investigator file as agreed upon prior to the trial start at each trial site.

No specific protocol data can be recorded directly in the eCRF without prior written or electronic record.

10.2 Electronic Case Report Form (eCRF)

An eCRF system provided by an independent third-party contract research organisation will be used for data capture. Contact details of the contract research organisation are provided in a trial-specific contact list. The system is validated and access at all levels to the system is granted/revoked following Ferring and vendor procedures, in accordance with regulatory and system requirements.

Data should be entered into the system within a reasonable time after source data is collected.

The investigator will approve/authorise the eCRF entries for each patient with an electronic signature which is equivalent to a handwritten signature.

The eCRF system and the database will be hosted at and administered by the independent third party contract research organisation. After the trial database is declared clean and released to the statistician, a final copy of the database will be stored at Ferring. The investigator will also receive a copy of the trial site's final and locked data (including audit trail, electronic signature and queries) as write-protected PDF-files produced and distributed by the independent third party contract

research organisation. The PDF-files will be stored on a CD and will be provided to the investigator before read access to the eCRF is revoked.

Modification of data entered into the eCRF will be captured in an electronic audit trail detailing the date and time of the correction and the user name of the person making the correction. Only site coordinator and investigator have privileges to modify data.

10.3 Data Management

A data management plan will be created under the responsibility of the Global Biometrics department at Ferring. The data management plan will be issued before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning, and validation.

The data management plan will describe capture methods, who is authorised to enter the data, decisions about ownership of data, source data storage, which data will be transferred (including timing of transfers), the origin and destination of the data, and who will have access to the data at all times.

10.4 Provision of Additional Information

On request, the investigators will provide Ferring with additional data relating to the trial, duly anonymised and protected in accordance with applicable requirements.

11 MONITORING PROCEDURES

11.1 Periodic Monitoring

The monitors will contact and visit the investigators periodically to ensure adherence to the protocol, International Conference of Harmonisation-Good Clinical Practice (ICH-GCP), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy and verifiability of eCRF entries compared to source data, verification of drug accountability, and compliance to safety reporting instructions. The investigators will permit the monitors direct access to all source data, including electronic medical records, and/or documents in order to facilitate data verification. The investigators will co-operate with the monitors to ensure that any discrepancies that may be identified are resolved. The investigators are expected to be able to meet the monitors during these visits. The first on-site monitoring visit will take place shortly after randomisation of the first patient. The frequency of the on-site monitoring visits is dependent on the number of enrolled patients at the trial site.

The source data verification process and definition of key variables to be monitored will be described in the trial-specific monitoring plan.

11.2 Audit and Inspection

The investigators will make all the trial-related source data and records available at any time to quality assurance auditor(s) mandated by Ferring, or to domestic/foreign regulatory inspector(s) or representative(s) from IECs/IRBs who may audit/inspect the trial.

The main purposes of an audit or inspection are to assess compliance with the trial protocol and the principles of ICH-GCP including the Declaration of Helsinki and all other relevant regulations.

The patients must be informed by the investigators and in the informed consent documents that authorised Ferring representatives and representatives from regulatory authorities and IECs/IRBs may wish to inspect their medical records. During audits/inspections the auditors/inspectors may copy relevant parts of the medical records. No personal identification apart from the screening/ randomisation number will appear on these copies.

The investigators should notify Ferring without any delay of any inspection by a regulatory authority or IEC/IRB.

11.3 Confidentiality of Patient Data

The investigators will ensure that the confidentiality of the patients' data will be preserved. In the eCRF or any other documents submitted to Ferring, the patients will not be identified by their names, but by an identification system, which consists of an assigned number in the trial. Documents that are not for submission to Ferring, e.g. the confidential patient identification code and the signed informed consent documents, will be maintained by the investigators in strict confidence.

12 CHANGES IN THE CONDUCT OF THE TRIAL

12.1 Protocol Amendments

Any change to this protocol will be documented in a protocol amendment, issued by Ferring, and agreed upon by the TSC, investigators, and Ferring prior to its implementation. Amendments may be submitted for consideration to the approving IECs/IRBs and regulatory authorities, in accordance with local regulations. Changes to the protocol to eliminate immediate hazard(s) to trial patients may be implemented prior to IECs/IRBs approval/favourable opinion.

12.2 Deviations from the Protocol

The investigators must inform the monitor if deviations from the protocol occur and the implications of the deviation must be reviewed and discussed. Any deviation must be documented, either as an answer to a query in the eCRF, in a protocol deviation report, or a combination of both. A log of protocol deviation reports will be maintained by Ferring. Protocol deviation reports and supporting documentation must be kept in the investigator's file and the trial master file.

12.3 Premature Trial Termination

Both the investigators (with regard to his/her participation) and Ferring reserve the right to terminate the trial at any time. Should this become necessary, the procedures will be agreed upon after consultation between the two parties. In terminating the trial, Ferring and the investigators will ensure that adequate consideration is given to the protection of the best interests of the patients. Regulatory authorities and IECs/IRBs will be informed.

In addition, Ferring reserves the right to terminate the participation of individual trial sites. Conditions that may warrant termination include, but are not limited to, insufficient adherence to protocol requirements and failure to enter patients at an acceptable rate.

13 REPORTING AND PUBLICATION

13.1 Clinical Trial Report

The data and information collected during this trial will be reported in a clinical trial report prepared by Ferring and submitted for comments and signature to the signatory investigators.

13.2 Confidentiality and Ownership of Trial Data

Any confidential information relating to the IMP or the trial, including any data and results from the trial will be the exclusive property of Ferring. The investigators and any other persons involved in the trial will protect the confidentiality of this proprietary information belonging to Ferring.

13.3 Publications and Public Disclosure

13.3.1 Publication Policy

Sponsor recognises and accepts that investigators may have a meaningful right to publish research results of the trial. Investigators must agree that the first publication of trial results is to be a joint publication covering all trial sites, and that subsequent publications will reference that primary publication. At the end of the trial, one or more manuscripts (including manuscripts, presentation, abstracts, posters etc.) for joint publication may be prepared in collaboration between the investigators and the TSC and Ferring, and the criteria for such publication shall be coordinated through the TSC. As the trial is a multi-centre trial, all publications shall be joint publications covering all trial sites unless specific written permission is obtained in advance from the TSC. However, if a joint manuscript has not been submitted for publication within 18 months of completion or termination of the trial, the investigators shall be free to publish separately. Any publication of results must acknowledge all trial sites.

Under the coordination of the TSC, authorship is granted based on the International Committee of Medicinal Journal Editors (ICMJE) criteria (see current official version: http/www.ICMJE.org).

Any external contract research organisation or laboratory involved in the conduct of this trial has no publication rights regarding this trial.

Any publication, whether joint or independent, on the results of the trial must be submitted in writing to the TSC and Ferring for comment prior to submission at least 60 days in advance of the submission of such proposed publication to the applicable journal or other forum in which the publication or presentation may be published or presented. At Ferring's request, the respective institution and/or investigator shall arrange for an additional delay in publication or presentation, not to exceed an additional 60 days, to enable Ferring to request deletion of Ferring Confidential Information and to arrange for filing of patent applications or other intellectual property protection. This statement does not give Ferring editorial rights over the content of a publication, other than to restrict the disclosure of Ferring's intellectual property. If the matter considered for publication is deemed patentable by Ferring, scientific publication will not be allowed until after a filed patent

application is published. Under such conditions the publication will be modified or delayed to allow sufficient time for Ferring to seek patent protection of the invention.

13.3.2 Public Disclosure Policy

ICMJE member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public, clinical trials registry. Thus, it is the responsibility of Ferring to register the trial in an appropriate public registry, i.e. www.ClinicalTrials.gov which is a website maintained by the National Library of Medicine at the U.S. National Institutes of Health. The trial will also be made publicly available at the EU Clinical Trials Register at www.clinicaltrialsregister.eu. Trial registration may occur in other registries in accordance with local regulatory requirements. A summary of the trial results is made publicly available in accordance with applicable regulatory requirements.

14 ETHICAL AND REGULATORY ASPECTS

14.1 Independent Ethics Committees or Institutional Review Boards

Independent ethics committees/institutional review boards will review the protocol and any amendments. The IECs/IRBs will review the patient information sheet and the informed consent form, their updates (if any), and any written materials given to the patients. A list of all IECs/IRBs to which the protocol has been submitted will be included in the clinical trial report.

14.2 Regulatory Authorities Authorisation / Approval / Notification

The regulatory permission to perform the trial will be obtained in accordance with applicable regulatory requirements. All ethical and regulatory approvals must be available before a patient is exposed to any trial-related procedure, including screening tests for eligibility.

14.3 End-of-Trial and End-of-Trial Notification

End of-trial is defined as the date of the last trial-related contact with the last patient ongoing in the trial. At the end-of-trial, Ferring shall notify the regulatory authorities and the IECs/IRBs in the participating countries about the completion of the clinical trial in accordance with national/local regulations.

14.4 Ethical Conduct of the Trial

This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki (World Medical Association, 2013), in compliance with the approved protocol, ICH-GCP, and applicable regulatory requirements.

14.5 Patient Information and Consent

Critically ill patients receiving care in the EDs/ICUs represent a highly vulnerable population with regard to informed consent as these patients are often not capable of participating in the consent process. Because of this, proxies are often required to provide consent and other health decisions for impaired patients.

The informed consent process in this trial will be obtained in accordance with national/local regulations.

The investigator (or the person delegated by the investigator) will obtain a freely given written consent in accordance with national/local regulations from each patient or his/her legally acceptable representative after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspects of the trial which are relevant to the patient's decision to participate. The patient or the legal representative should be given ample time to consider participation in the trial, before the consent is obtained. The patient (and the legal representative, if applicable) will receive a copy of the patient information and the signed informed consent form.

The investigator (or the person delegated by the investigator) will explain that it is completely free to refuse to enter the trial or to withdraw from trial at any time, without any consequences for the patient's further care and without the need to justify the decision.

The investigator (or the person delegated by the investigator) will inform that the monitor(s) and quality assurance auditor(s) mandated by Ferring, IRB/IEC representatives, or regulatory authority inspector(s), in accordance with applicable regulatory requirements, may review the patient's source records and data. Data protection will be handled in compliance with the national/local regulations.

If new information becomes available that may be relevant to the willingness to continue participation in the trial, a new patient information and informed consent form will be forwarded to the IECs/IRBs and the regulatory authorities, if required. The trial patients (and the legal representatives, if applicable) will be informed about this new information and re-consent will be obtained.

14.6 Patient Information Card

If required by local regulations, the patient will be provided with a patient information card bearing required trial-related information.

Each patient's primary care physician will be notified of their participation in the trial by the investigator, if the patient agrees.

14.7 Compliance Reference Documents

The Helsinki Declaration, the consolidated ICH-GCP, the European Union Clinical Trials Directive, 21 CFR Part 312, and other national laws in the countries where the trial takes place shall constitute the main reference guidelines for ethical and regulatory conduct.

15 LIABILITIES AND INSURANCE

15.1 ICH-GCP Responsibilities

The responsibilities of Ferring, the monitors, and the investigators are defined in the ICH-GCP consolidated guideline, and applicable regulatory requirements in the country where the trial takes place. The investigators are responsible for adhering to the ICH-GCP responsibilities of investigators, for dispensing the IMP in accordance with the approved protocol or an approved amendment, and for its secure storage and safe handling throughout the trial.

15.2 Liabilities and Insurance

In case of any damage or injury occurring to a patient in association with the IMP or the participation in the trial, Ferring has contracted an insurance which covers the liability of Ferring, the investigators, and other persons involved in the trial in compliance with the laws in the countries involved.

16 ARCHIVING

16.1 Investigator File

The investigator is responsible for maintaining all the records, which enable the conduct of the trial at the site to be fully understood, in compliance with ICH-GCP. The trial documentation including all the relevant correspondence should be kept by the investigator for at least 15 years (or longer if so required by local law) after the completion or discontinuation of the trial, if no further instructions are given by Ferring.

The investigator is responsible for the completion and maintenance of the confidential patient identification code which provides the sole link between named patient source records and anonymous eCRF data for Ferring. The investigator must arrange for the retention of this patient identification log and signed informed consent documents for at least 15 years (or longer if so required by local law) after the completion or discontinuation of the trial.

No trial site document may be destroyed without prior written agreement between the investigator and Ferring. Should the investigator elect to assign the trial documents to another party, or move them to another location, Ferring must be notified. If the investigator retires and the documents can no longer be archived by the site, Ferring can arrange having the investigator file archived at an external archive.

16.2 Trial Master File

Ferring will archive the trial master file in accordance with ICH-GCP and applicable regulatory requirements.

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