Supplementary Online Content 2

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Collaborators

The Selepressin Evaluation Program for Sepsis-Induced Shock - Adaptive Clinical Trial (SEPSIS-ACT) Investigators

A total of 63 sites were activated and authorized to recruit patients for the trial in a total of 5 countries; principal site investigators are listed in italics.

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Trial Steering Committee (TSC)

Derek C. Angus (chair)[1], Pierre-Francois Laterre[2], Roger J. Lewis[3], James A. Russell[4], Steven Opal[5], Donald M. Yealy[1], Bruno François[6], Anders Perner[7], Peter Pickkers[8], Jan Carlsen[9], Nis Agerlin Windeløv[9], Karsten Jacobsen[9], Allan Blemings[9], Anne Louise Kjølbye[9]

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Limoges, France; [7]Rigshospitalet, Copenhagen, Denmark; [8]Radboud University Nijmegen Medical Centre Nijmegen, The Netherlands; [9]non-voting representatives of sponsor

Data and Safety Monitoring Board (DSMB)

Arthur S. Slutsky (chair)[1], Stephen Senn[2], Boyd Taylor Thompson[3], William Barsan[4], Timothy Evans[5], Marcus J. Schultz[6]

[1]St- Michel's Hospital, Toronto, Canada; [2]Luxemburg Institute of Health, Strassen, Luxembourg; [3]Massachusetts General Hospital, Boston, Massachusetts; [4]University of Michigan, Ann Arbor, Michigan; [5]Royal Brompton Hospital, London, UK, member of the DSMB till December 2016; [6]University of Amsterdam, Amsterdam, The Netherlands, member of the DSMB from January 2017

Clinical Coordinating Centers

To ensure, as far as possible, that only eligible patients entered the trial, all potential patients were discussed with one of the assigned clinical coordinating centers (CCCs) prior to randomization. The CCCs were available 24 hours a day throughout the trial to answer investigators' medical questions (such as assessment of eligibility and medical support).

Ocean State Clinical Coordinating Center: Steven Opal[1], Mitchell Levy[1], Nicholas Ward[1], Andre Kalil[2], Patricia A. Cristofaro[3], Russell J. McCulloh[4]

St. Luc Clinical Coordinating Center: Pierre Francois Laterre[5], Xavier Wittebole[5], Thierry Dugernier [7]

[1]Alpert Medical School of Brown University, Providence, Rhode Island; [2]University of Nebraska Medical Center, Omaha, Nebraska; [3]Providence Veteran Affairs Medical Center, Providence, Rhode Island; [4]Children's Mercy Kansas City, Kansas City, Missouri; [5]Cliniques Universitaires Saint-Luc, Brussels, Belgium; [6]Clinique Saint-Pierre, Ottignies-Louvain-la-Neuve, Belgium

Supplementary methods

Eligibility criteria

The intention was to enroll a typical sample of patients presenting with septic shock and commence treatment with the investigational medicinal product (IMP; aka 'study drug') 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 persisted for at least one hour. The exact criteria used for the screening of eligible patients are listed below with the explanatory text, as presented in the protocol, in italics.

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 liter 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 ('study drug') 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 liter of fluid for hypotension to start the randomization process balances the need to ensure that patients have been properly fluid resuscitated while still allowing for early enrollment 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).

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.

   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, hemorrhage, burns, or congestive heart failure/cardiogenic shock).

3. Previous severe sepsis with intensive care unit (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 ischemia.

   Selepressin is a potent V1a agonist and V1a-induced mesenteric vasoconstriction is a safety concern so patients with known or suspected acute mesenteric ischemia 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.

   V1a 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 chronic obstructive pulmonary disease (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 enrollment 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-enrollment in a non-investigational trial requires preapproval of the TSC and will be assessed on a case by case basis. In principle, co-enrollment is allowed unless it is expected to impact the outcome of this clinical trial.

Eligibility criteria – post-randomization / before start of study drug infusion

In addition, the following criteria must be met at start of study drug 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.

Study endpoints

Primary endpoint - vasopressor- and ventilator-free days (VV-free days) 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 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 VV-free days, 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 VV-free days). 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 COPD or sleep apnea does not count as mechanical ventilation (regardless of pressure).

Key secondary endpoints

- All-cause mortality (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 randomization)
- 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 randomization)
- 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 (see description of modified SOFA below)
- 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 - these data were collected but have not been analyzed
- 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

The following additional endpoints were specified in the study protocol but were not conducted because the trial was stopped at the end of Part 1.

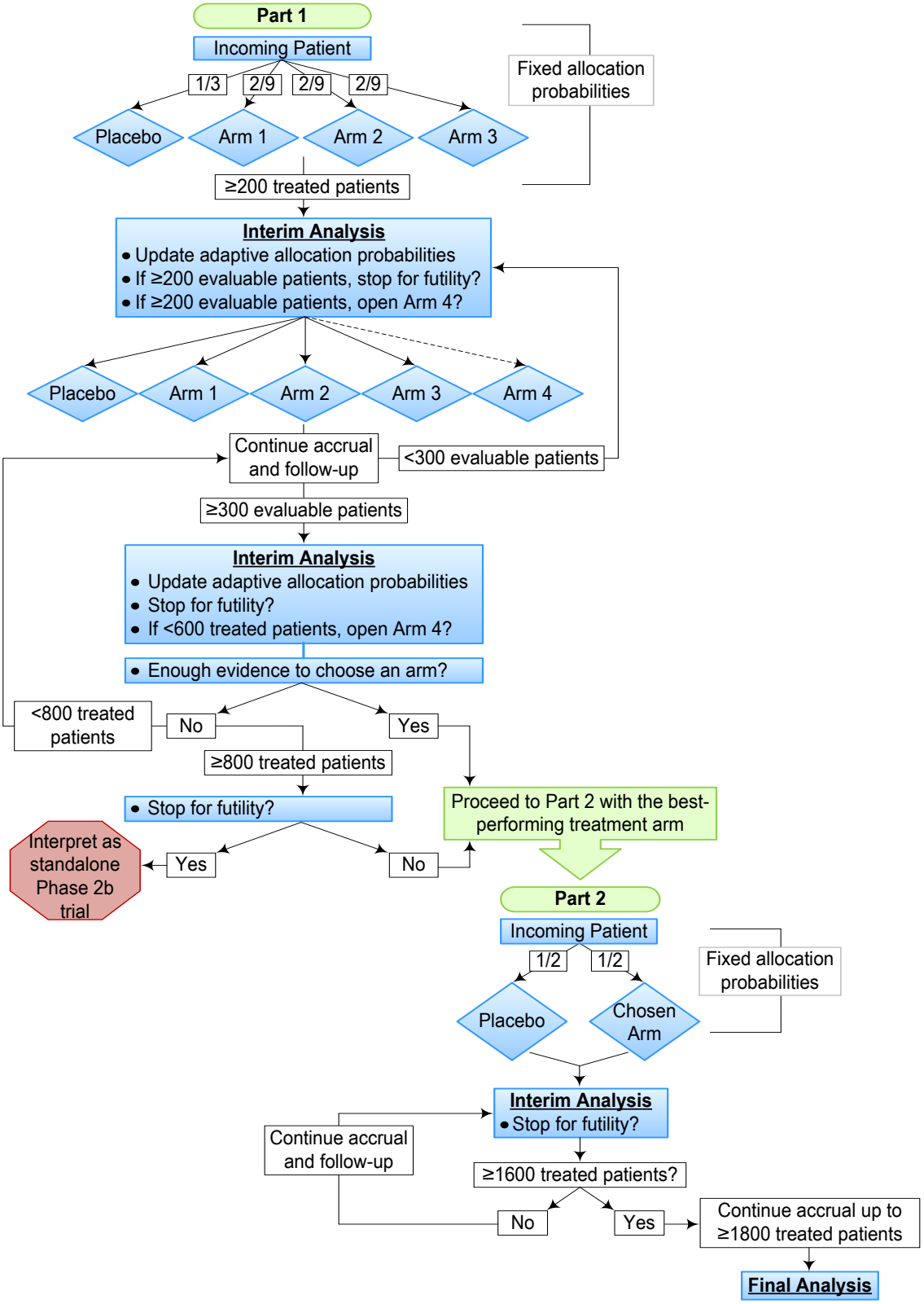
- Pharmacokinetic response (in a subset of approximately 200 patients) - to be reported separately according to a pre-specified pharmacokinetic analysis plan
- Creatinine clearance
- Ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2 ratio) (in a subset of 100-350 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)

Modified Sequential Organ Failure Assessment (SOFA) score

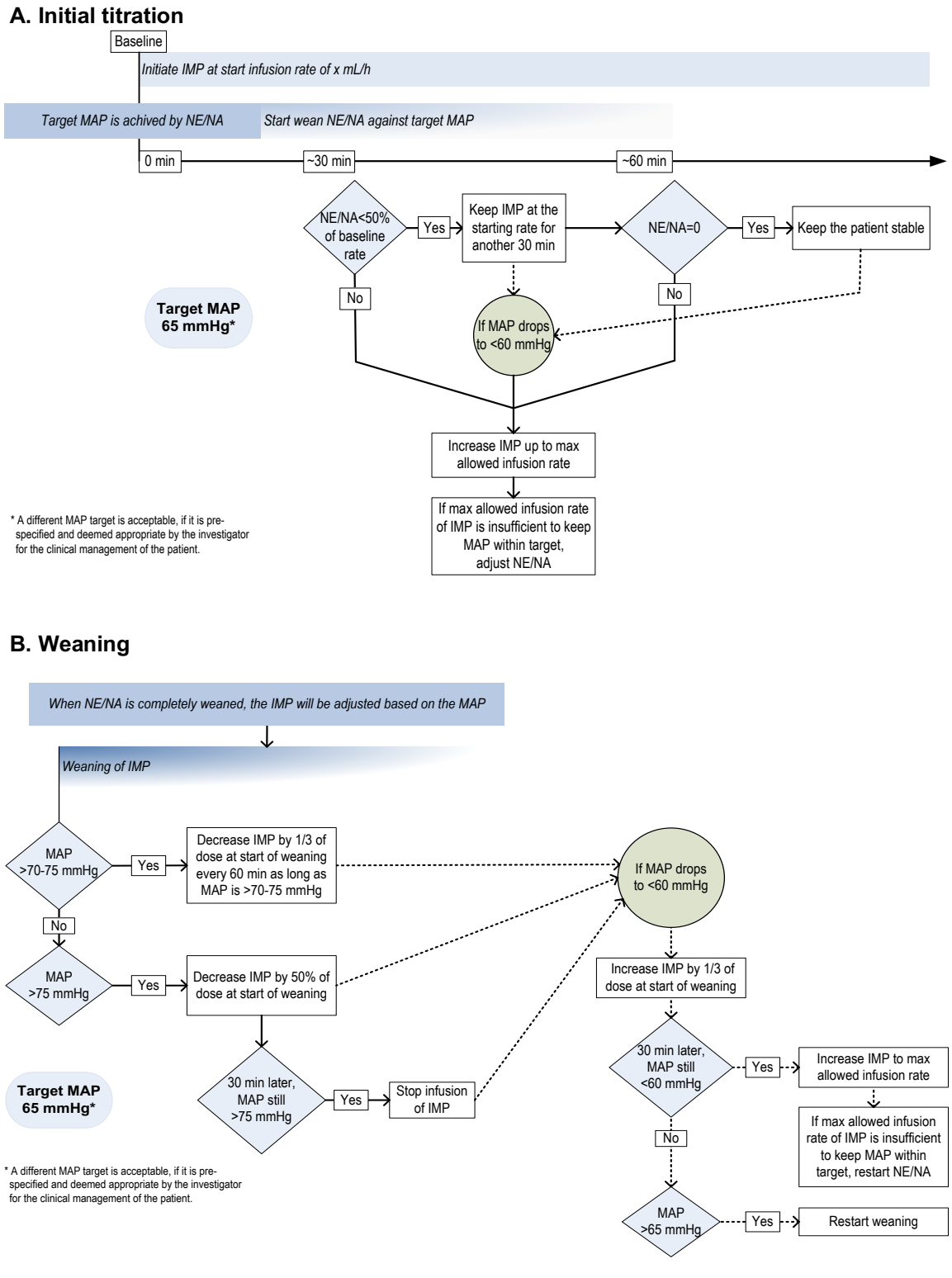
A modified version of the SOFA was used (i.e., SOFA except the Glasgow Coma Scale). As many patients are sedated due to mechanical ventilation a meaningful assessment of the neurological function using the Glasgow Coma Scale cannot be performed. In addition, any dose of IMP, vasopressin, terlipressin,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

Supplementary Figures and Tables

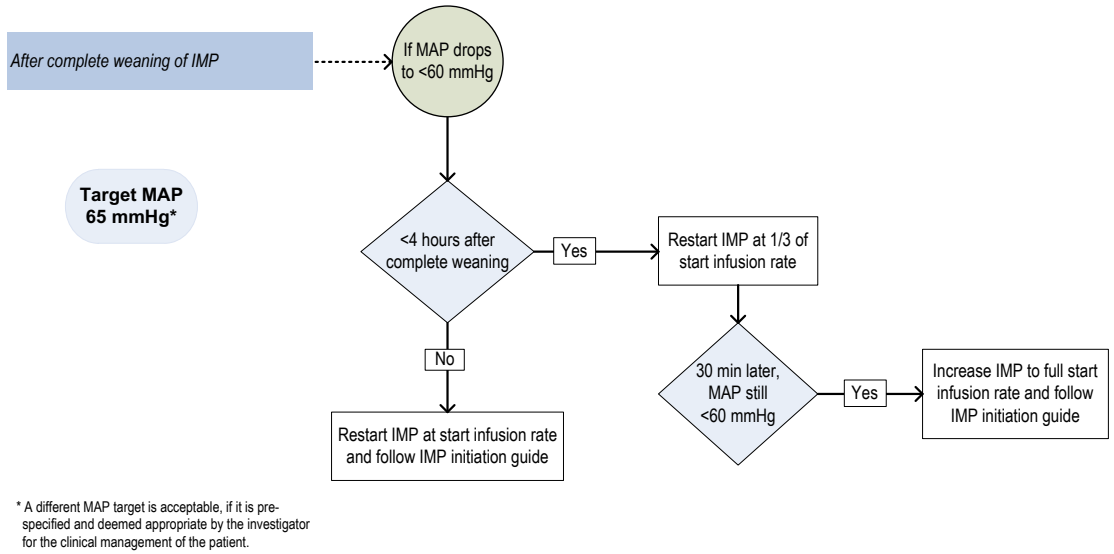
eFigure 1. Response adaptive design overview



eFigure 2. Investigational medicinal product (IMP; 'study drug') titration, stop and restart

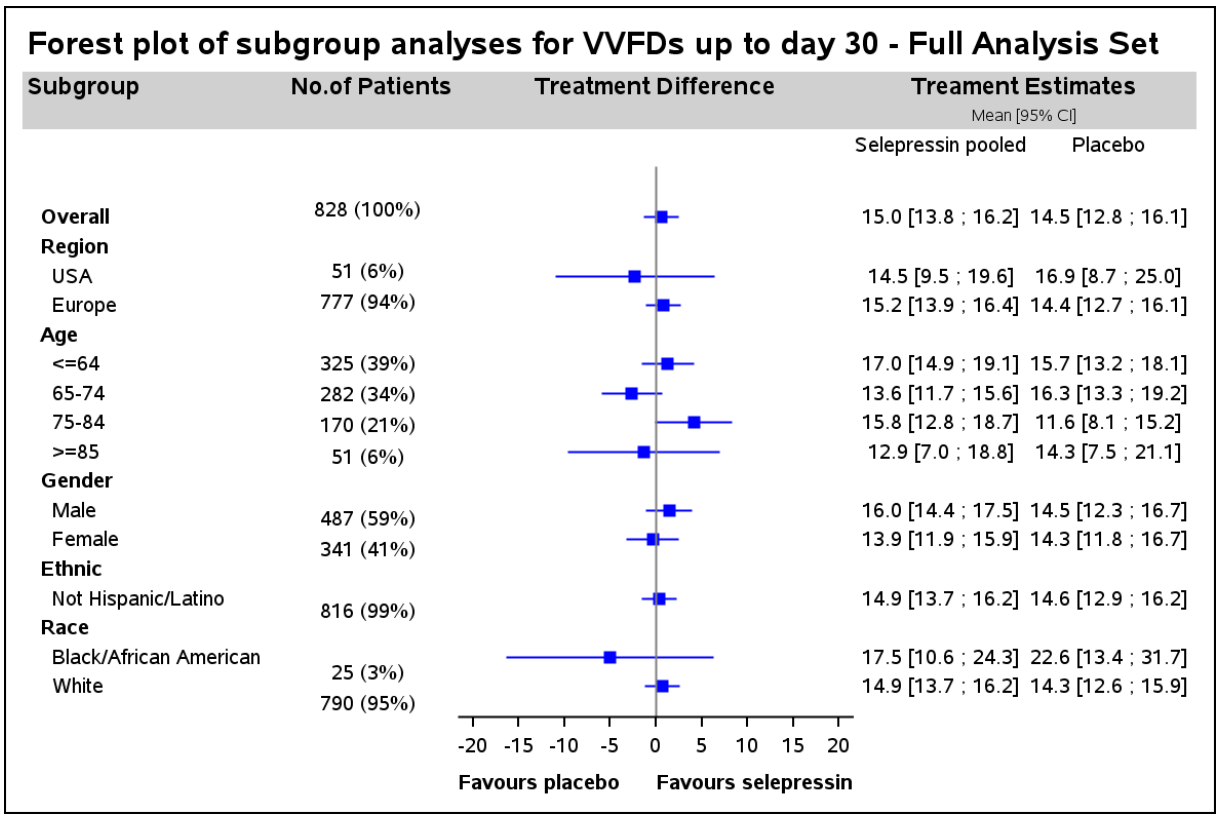


C. Re-starting



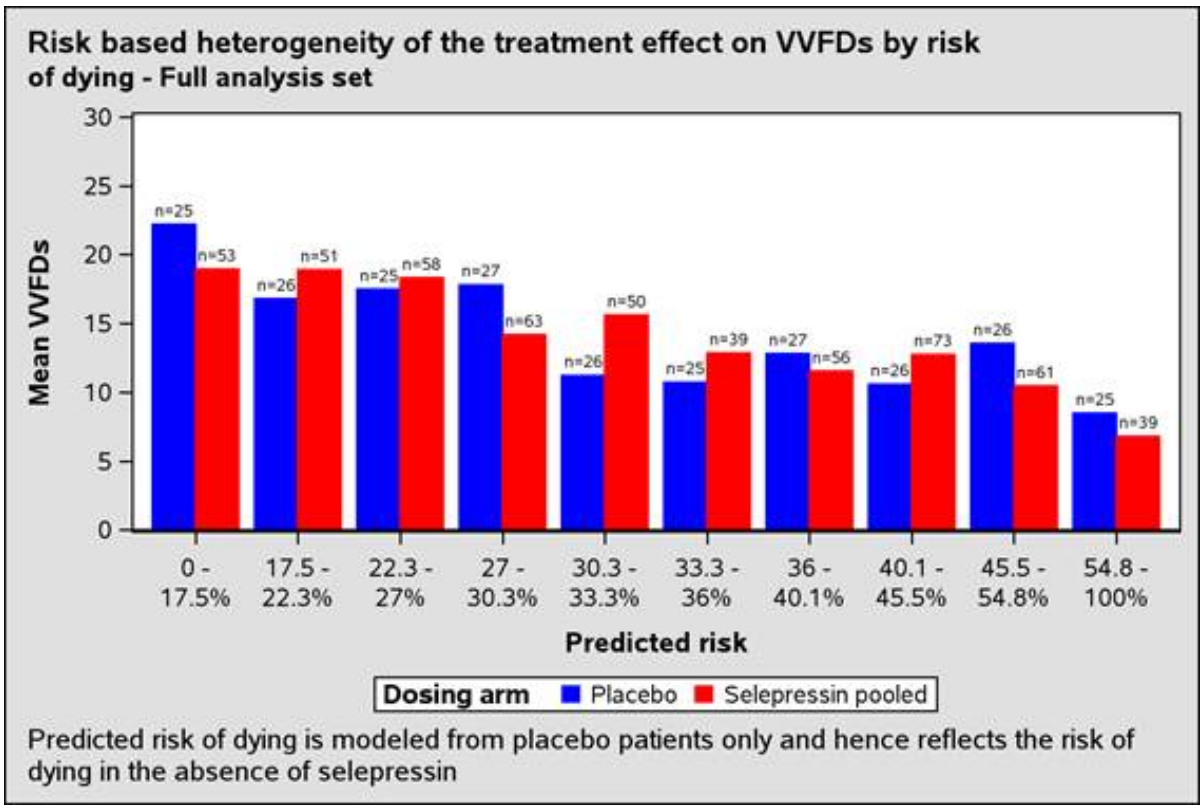
Treatment algorithm for A. - initiation of the IMP, B. - weaning the IMP, and C. - restarting the IMP. Mean Arterial blood Pressure (MAP), Investigational Medicinal Product (IMP, aka 'study drug'), norepinephrine/noradrenaline (NE/NA). Baseline denotes start of the IMP infusion.

eFigure 3. Demographic subgroup analyses



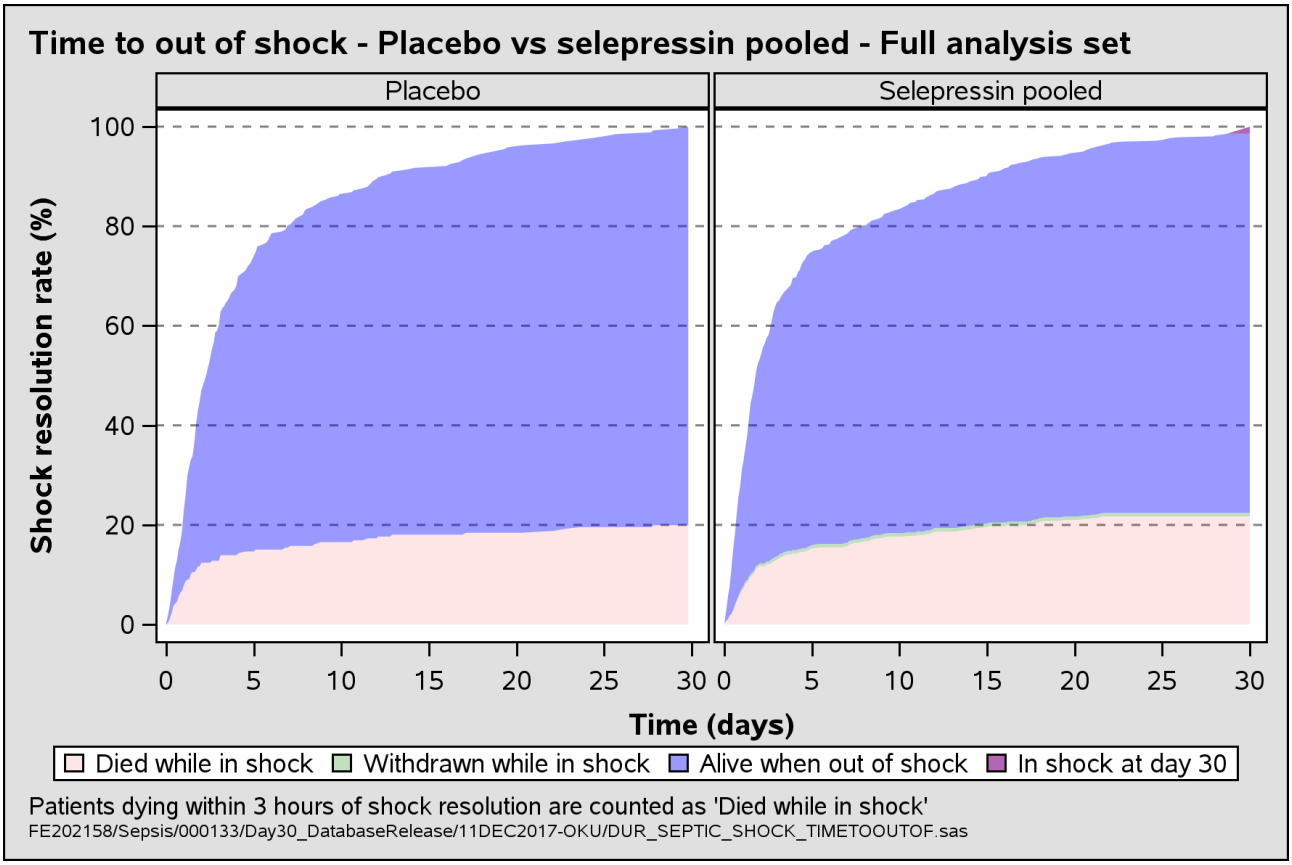
eFigure 3 depicts the treatment effects for the primary endpoint of Vasopressor and Ventilator Free Days (VVFDs) for predefined demographic subgroups. Age in years; Europe represent patients from Belgium, Denmark, France and the Netherlands. Treatment estimates are mean values corrected for baseline parameters with 95% confidence intervals.

eFigure 4. Risk based heterogeneity of the treatment effect per risk of death



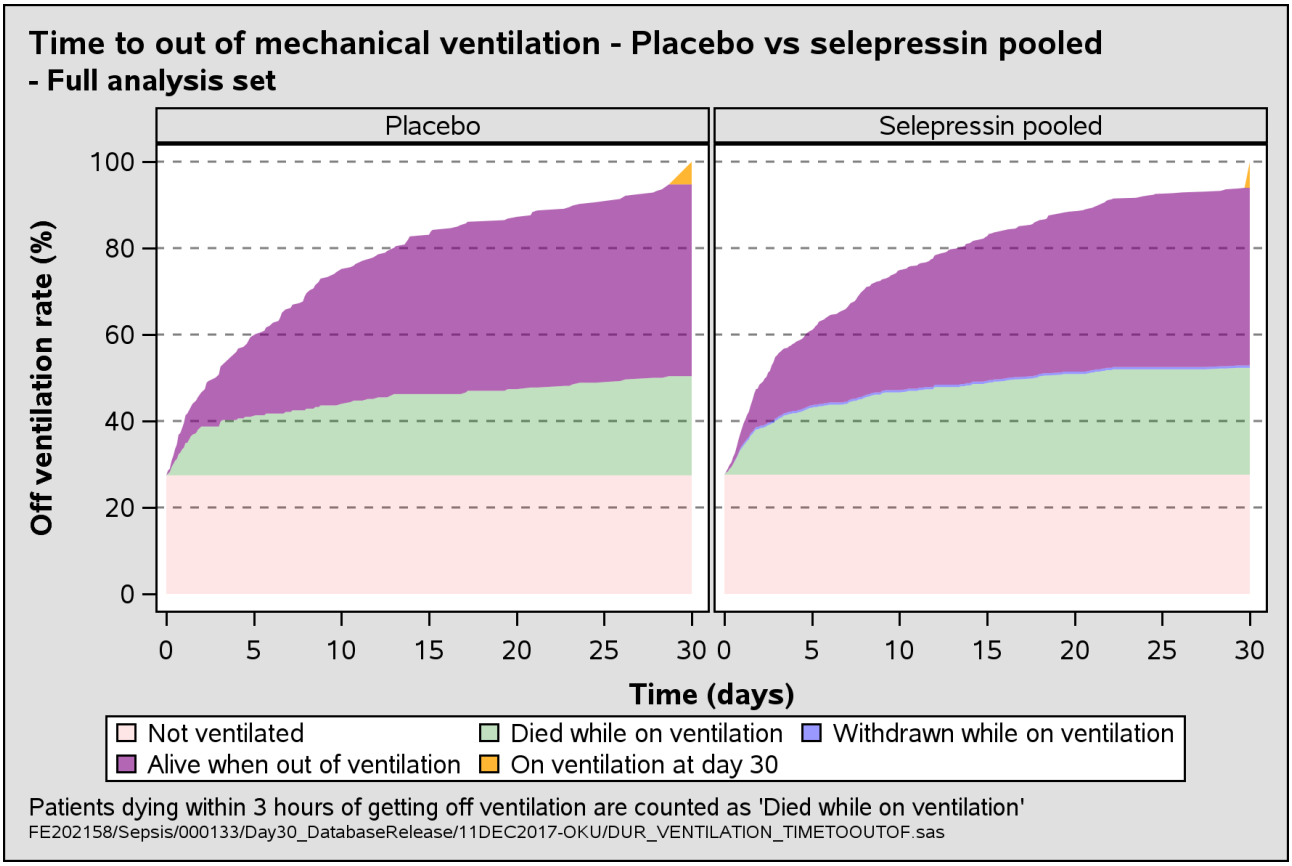
eFigure 4 depicts the primary endpoint of Vasopressor and Ventilator Free Days (VVFDs) by strata of estimated risk of death. The risk of death was estimated by a predictive model incl. age, individual SOFA score components and 30 day mortality rate for the placebo group.

eFigure 5. Time to out of shock



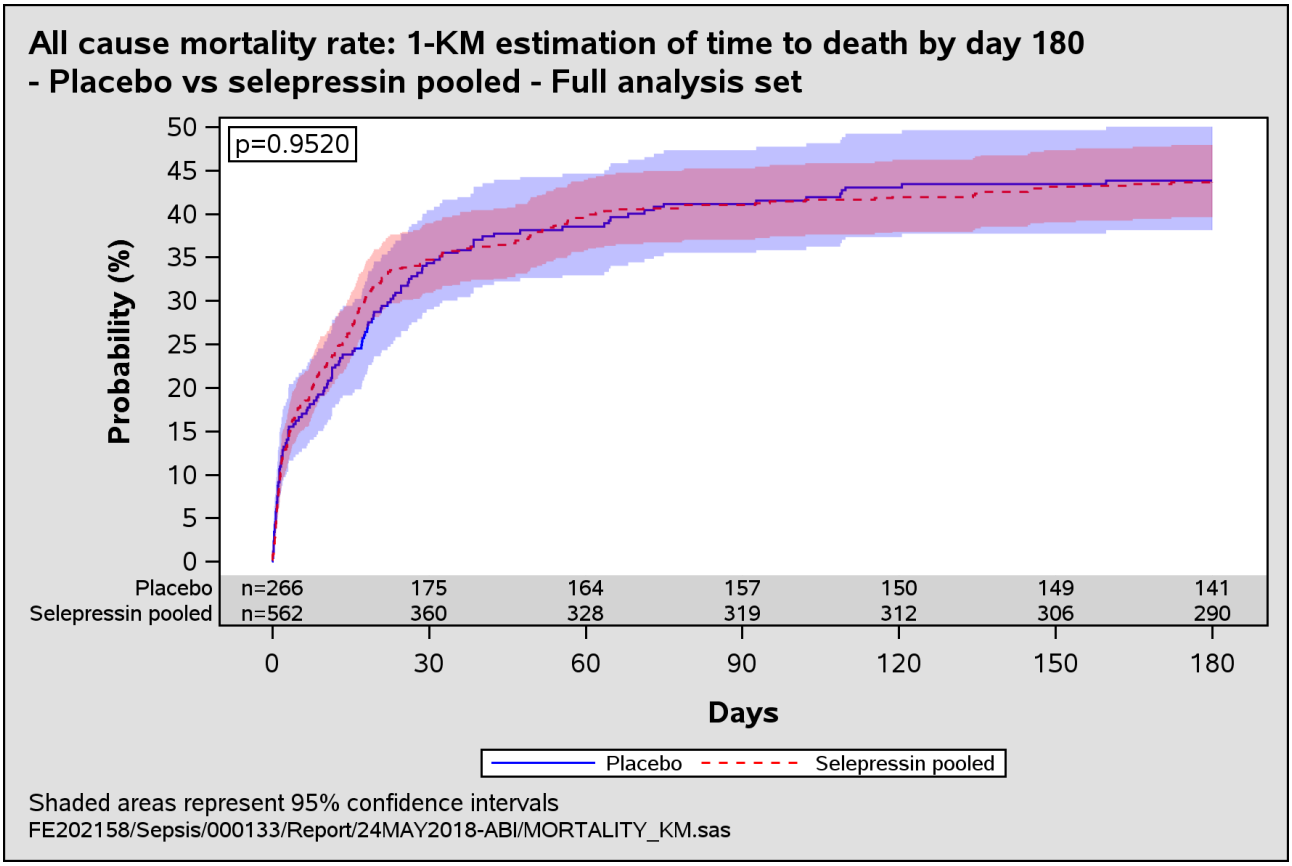
eFigure 5 depicts the accumulated probability of being out of shock (i.e., not receiving vasopressor treatment) from start of the investigational medicine product to day 30 including other reasons for not being registered as receiving vasopressor treatment (incl. died while on vasopressor therapy, withdrawn from trial while receiving vasopressor treatment, receiving vasopressor therapy at the end of the 30 day registration period).

eFigure 6. Time to out of mechanical ventilation



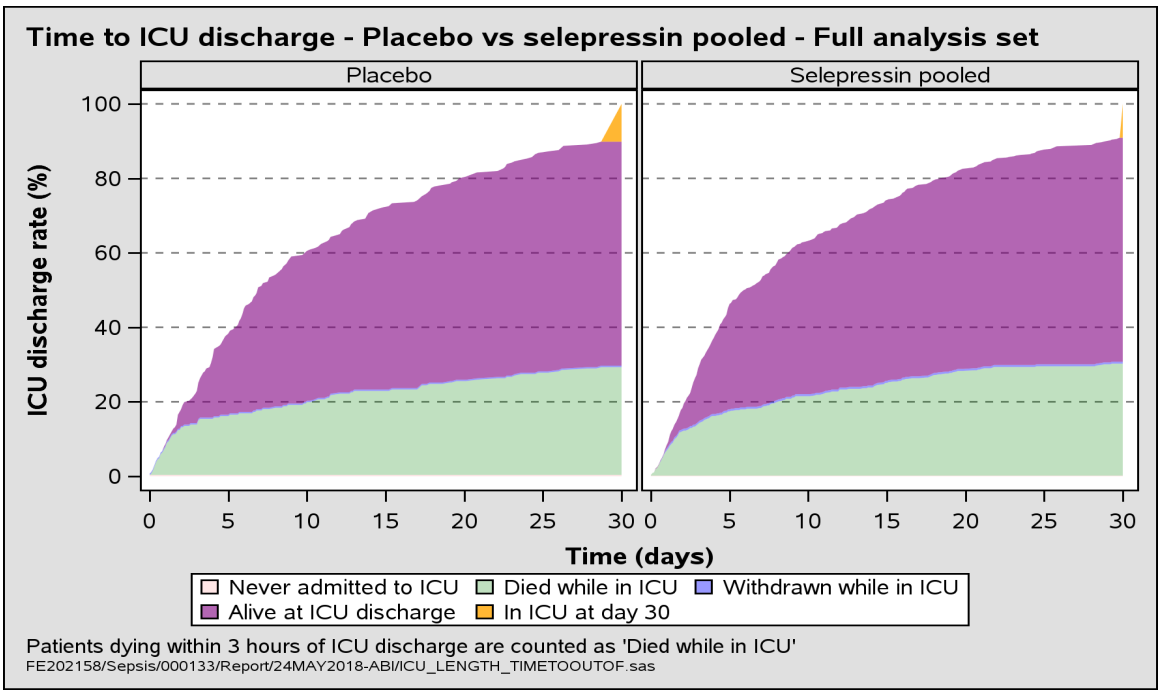
eFigure 6 depicts the accumulated probability of being off mechanical ventilator therapy over time from start of the investigational medicine product to day 30 including other reasons for not being registered as receiving mechanical ventilator therapy (incl. died while receiving mechanical ventilator therapy, withdrawn from trial while receiving mechanical ventilator therapy, and receiving mechanical ventilator therapy end of the 30 day registration period).

eFigure 7. All-cause mortality to day 180

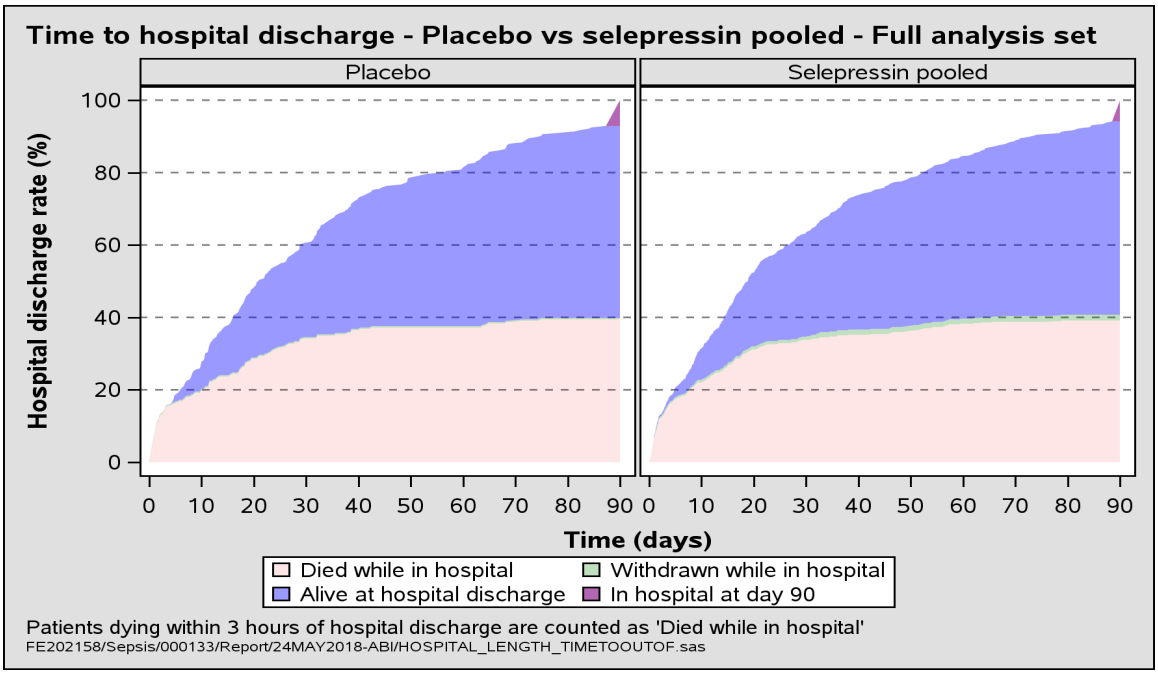


eFigure 7 depicts a Kaplan-Meier (KM) plot of the accumulated probability of death in the first 180 days following start of the investigational medicine product. "n=" denotes the number of patients at risk (alive and in the trial) at 30 days intervals.

eFigure 8. Time to ICU and hospital discharge

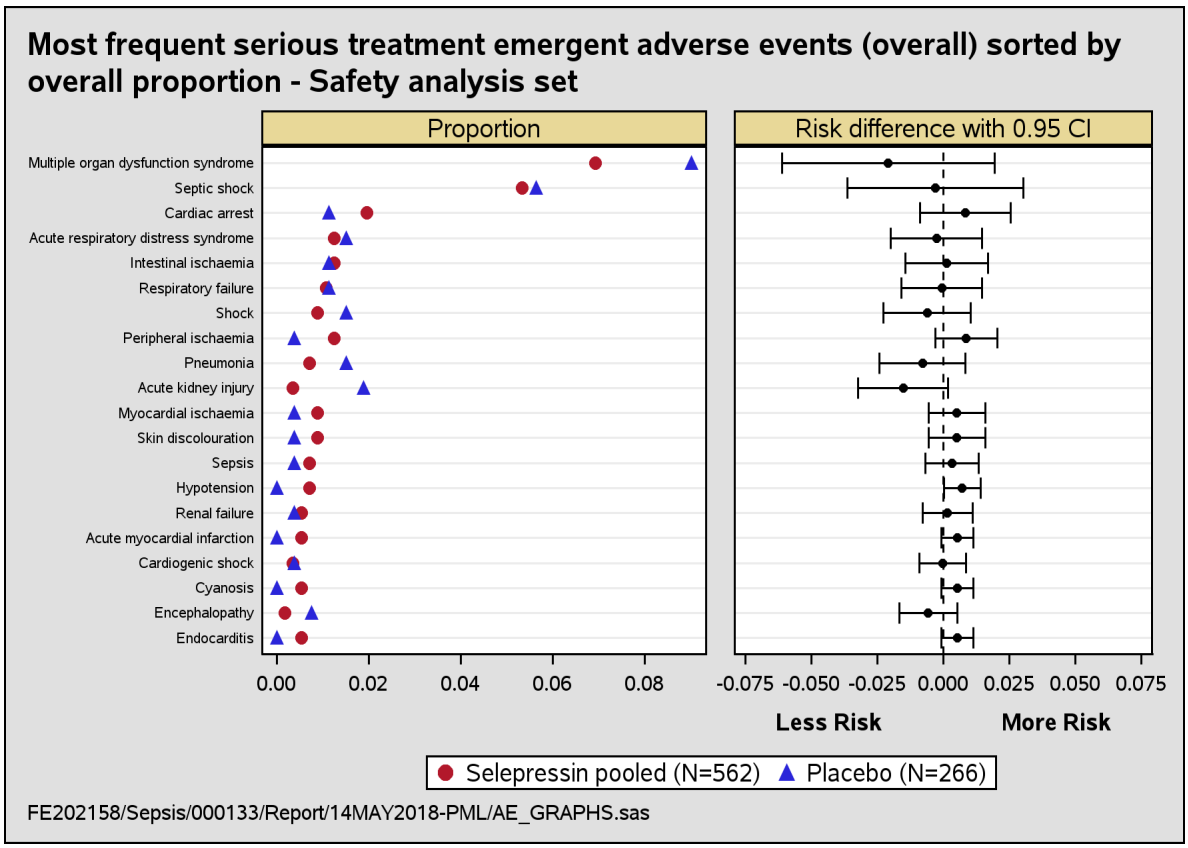


eFigure 8a depicts the accumulated probability of being out of the ICU and without readmission over time from start of the investigational medicine product to day 30 taking competing risks into account (incl. died while in the ICU, withdrawn from trial prior to ICU discharge, and in the ICU at the end of the 30 day registration period).



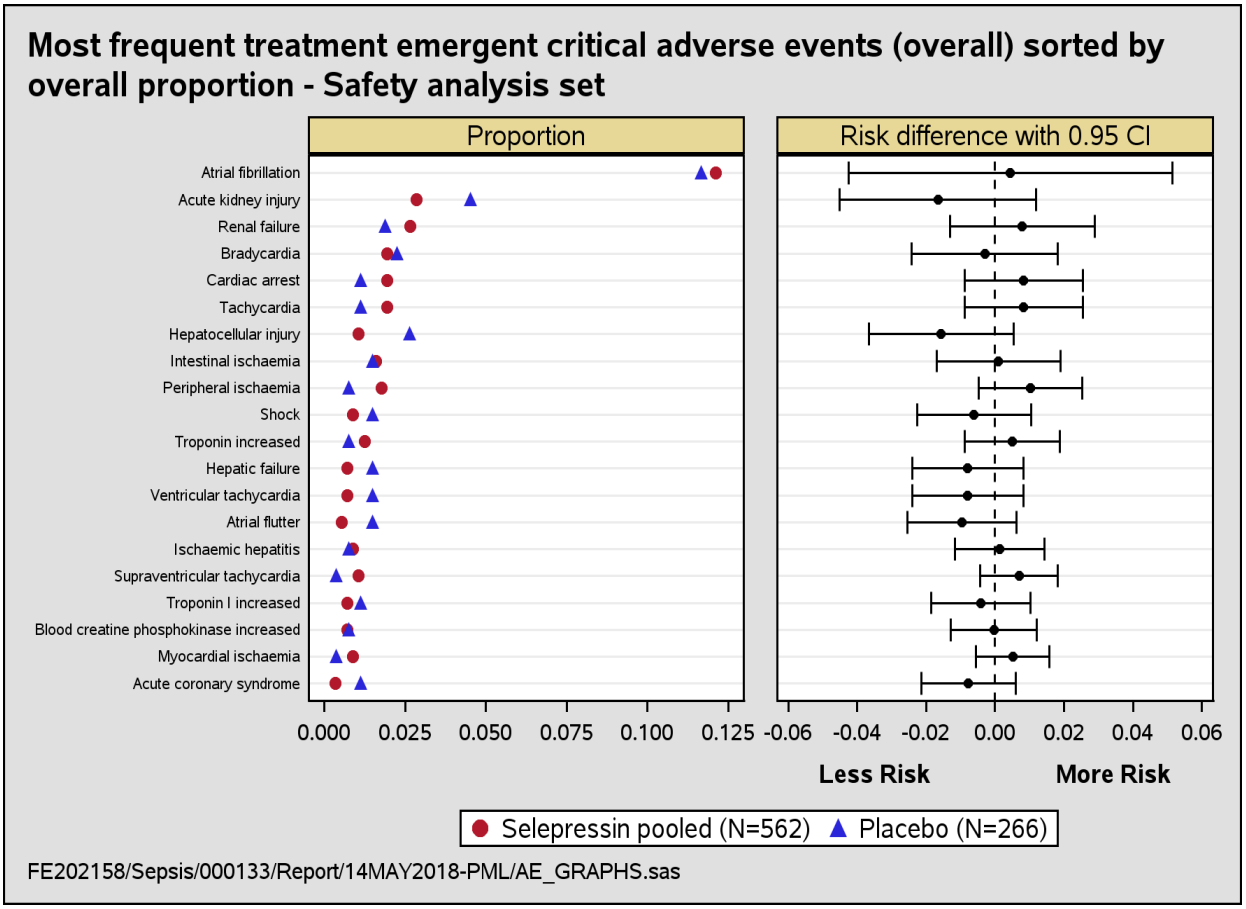
eFigure 8b depicts the accumulated probability being out of the hospital without readmission over time from start of the investigational medicine product to day 90 taking competing risks into account (incl. died while in hospital, withdrawn from trial before hospital discharge, and still in hospital at the end of the 90 day registration period).

eFigure 9. Most frequent serious adverse events



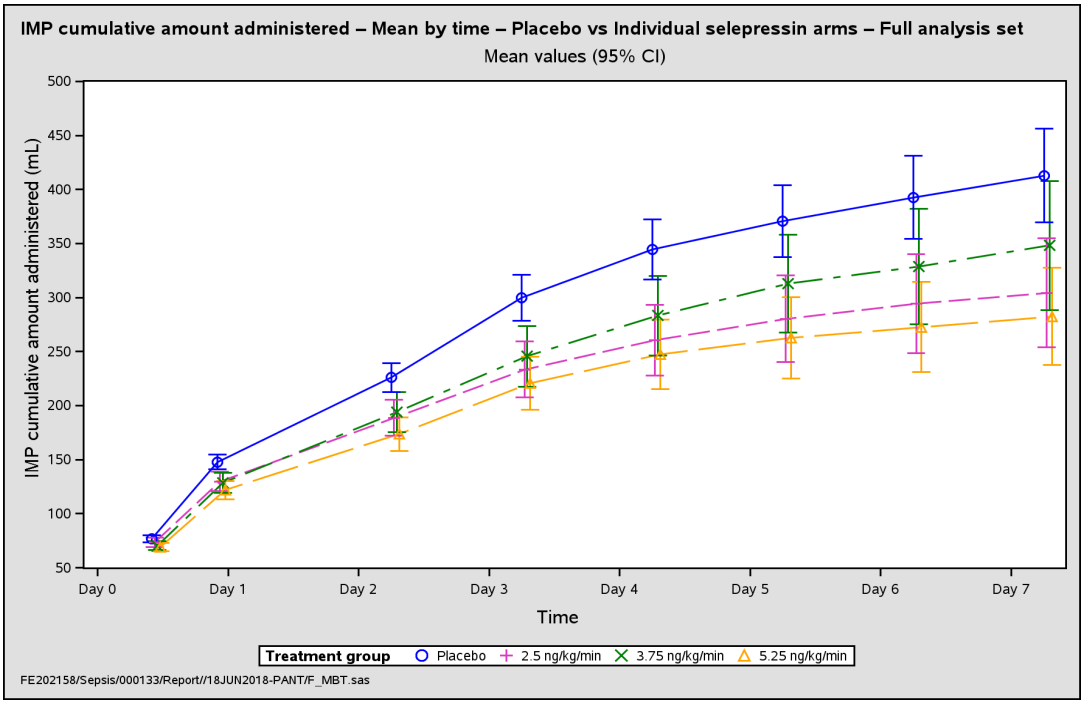
eFigure 9 depicts the proportion (left) and difference in proportions (risk difference, right) of the 20 most frequent serious adverse event for patients allocated to the selepressin group and the placebo group, respectively.

eFigure 10. Events of special interest

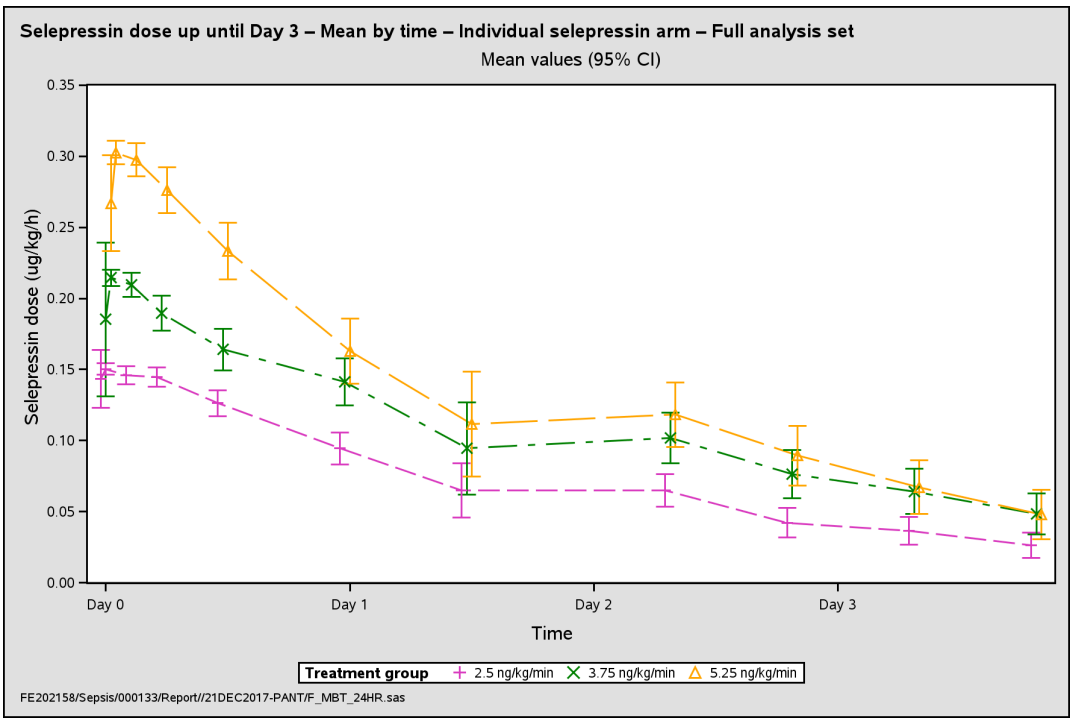


eFigure 10 depicts the proportion (left) and difference in proportions (risk difference, right) of predefined adverse events of special interest (critical adverse events) for patients allocated to the selepressin group and the placebo group, respectively.

eFigure 11. Administration of study drug by volume and dose

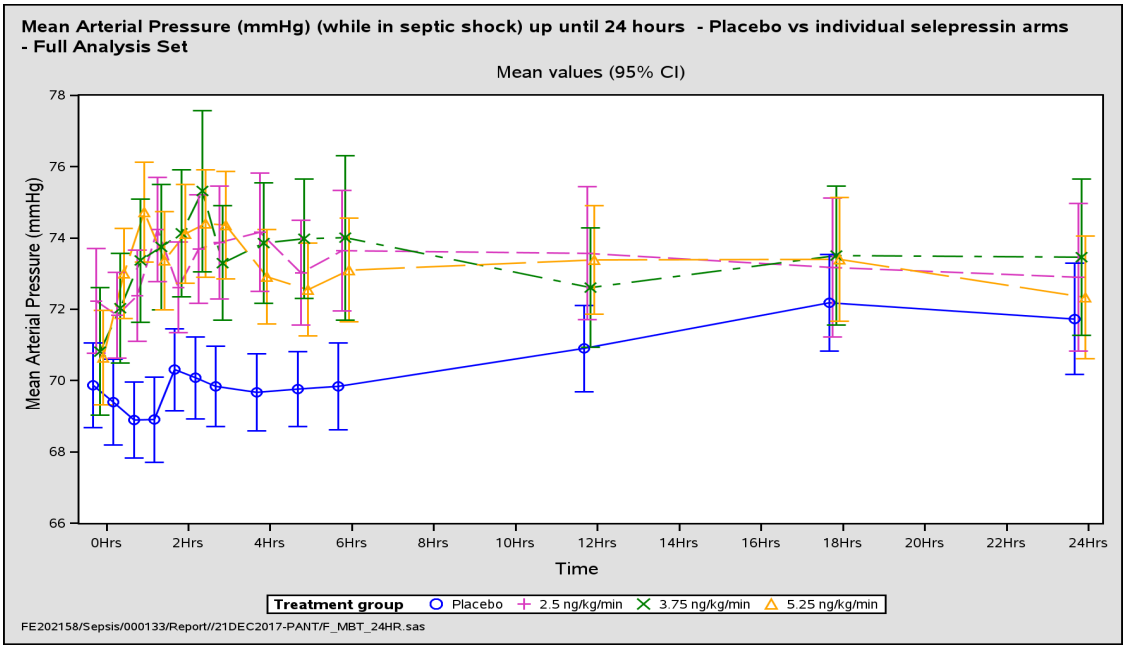


eFigure 11a depicts the accumulated volume of blinded Investigational Medicinal Product (IMP, 'study drug'), placebo or selepressin, infused over the first 7 days of treatment in ascending concentrations.

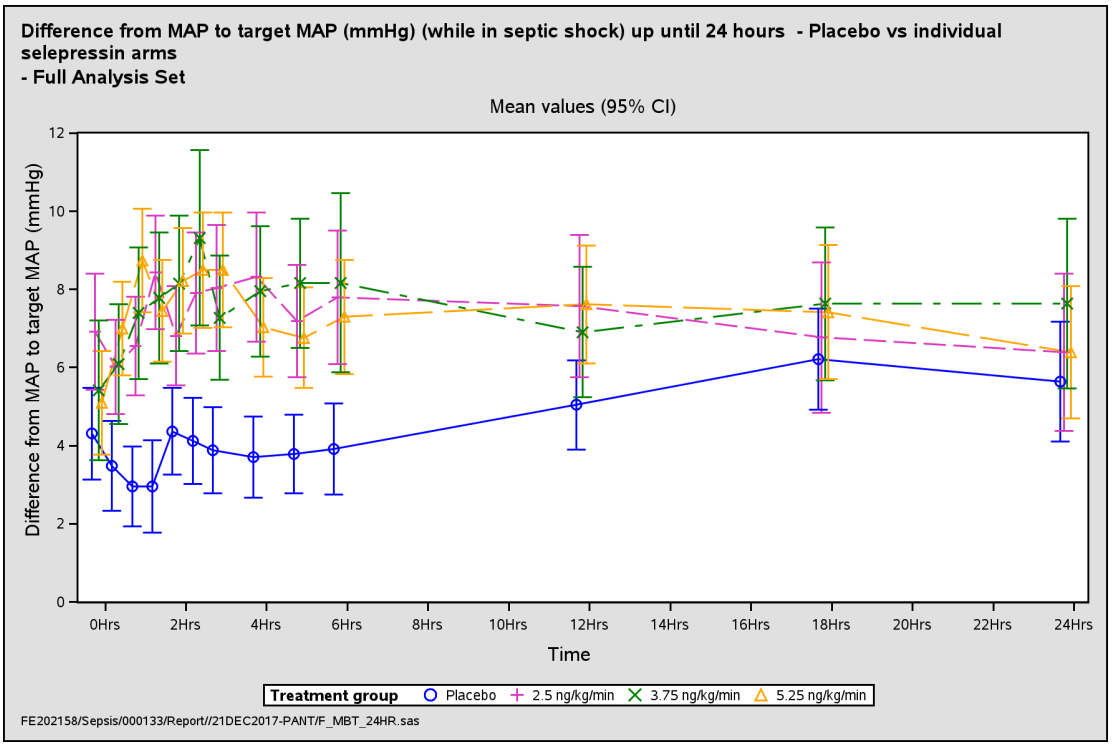


eFigure 11b depicts the dose of selepressin administered per hour for the first 4 days of treatment (i.e. up to end of day 3). The solution for infusion was prepared in a blinded manner with a concentration corresponding to the allocated dosing regimen of the patient.

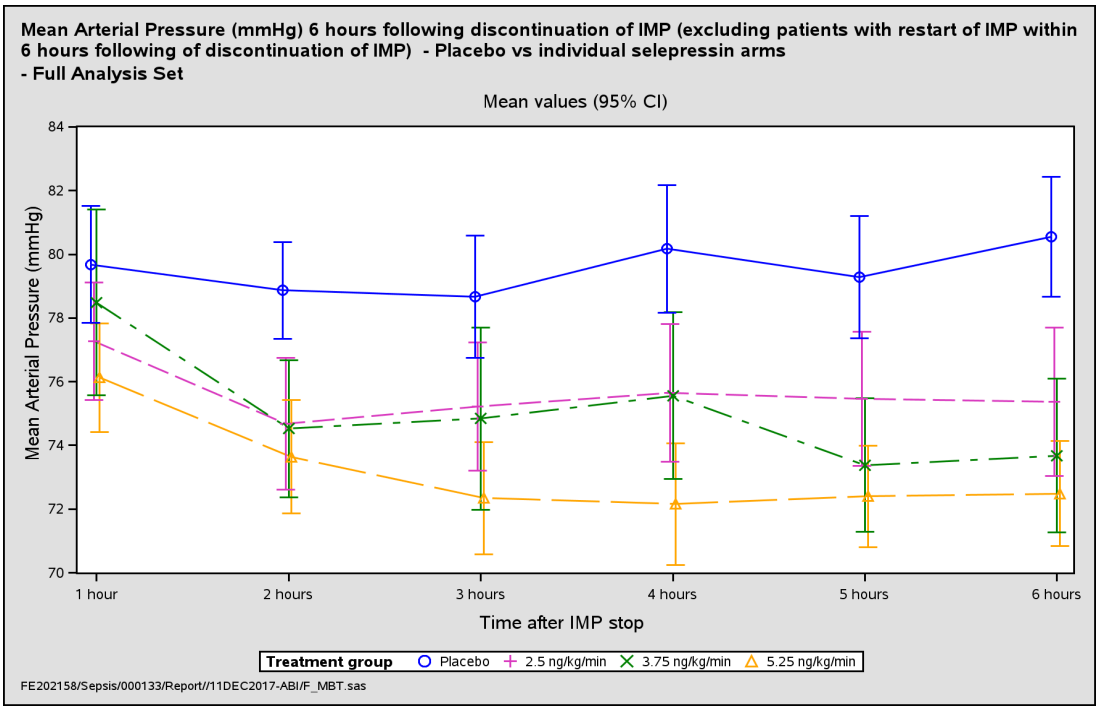
eFigure 12. Mean arterial pressure by treatment group



eFigure 12a depicts the mean arterial blood pressure (MAP) over the first 24h for patients alive and still on vasopressor treatment (i.e. while in septic shock).

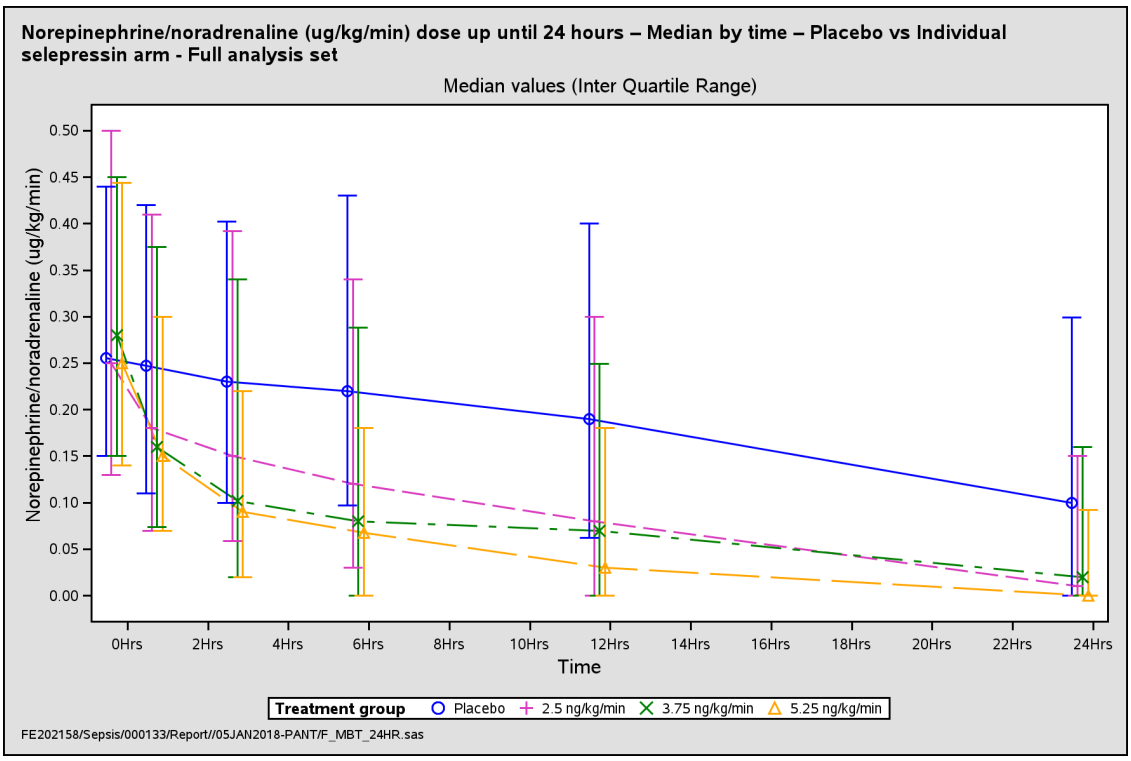


eFigure 12b depicts the difference in the patient's mean arterial blood pressure (MAP) to the targeted blood pressure (MAP target) of the patient. The default MAP target was 65mmHg but could be adjusted according to the need of the patient if pre-specified and deemed appropriate by the investigator.

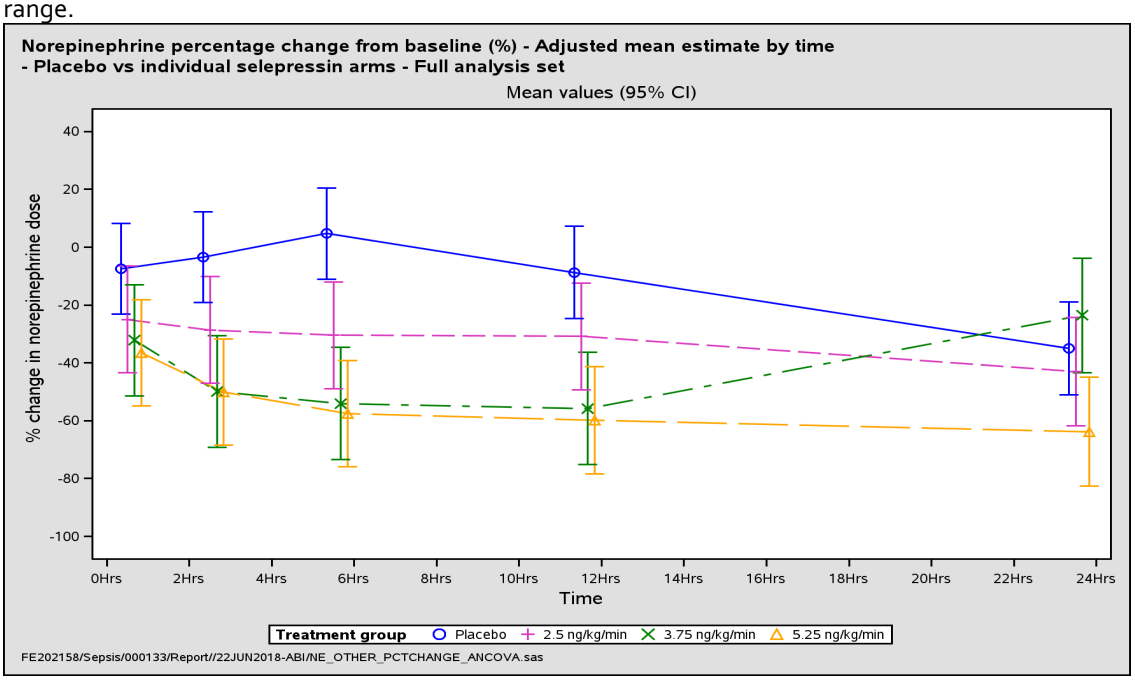


eFigure 12c depicts the mean arterial blood pressure (MAP) for the first 6 hours after stop of the Investigational Medicinal Product (IMP, aka 'study drug').

eFigure 13. Norepinephrine administration

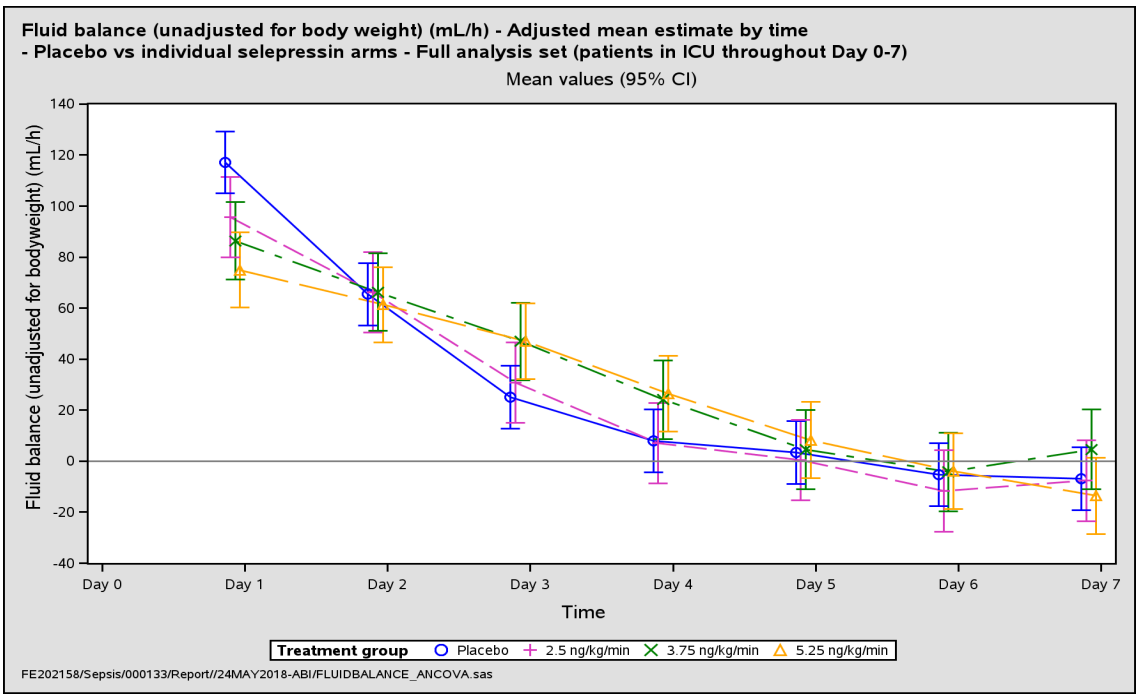


eFigure 13a depicts the median dose of open-label norepinephrine/noradrenaline administered over the first 24 hours after start of the Investigational Medicinal Product (IMP,'study drug'). Whiskers denote interquartile range.

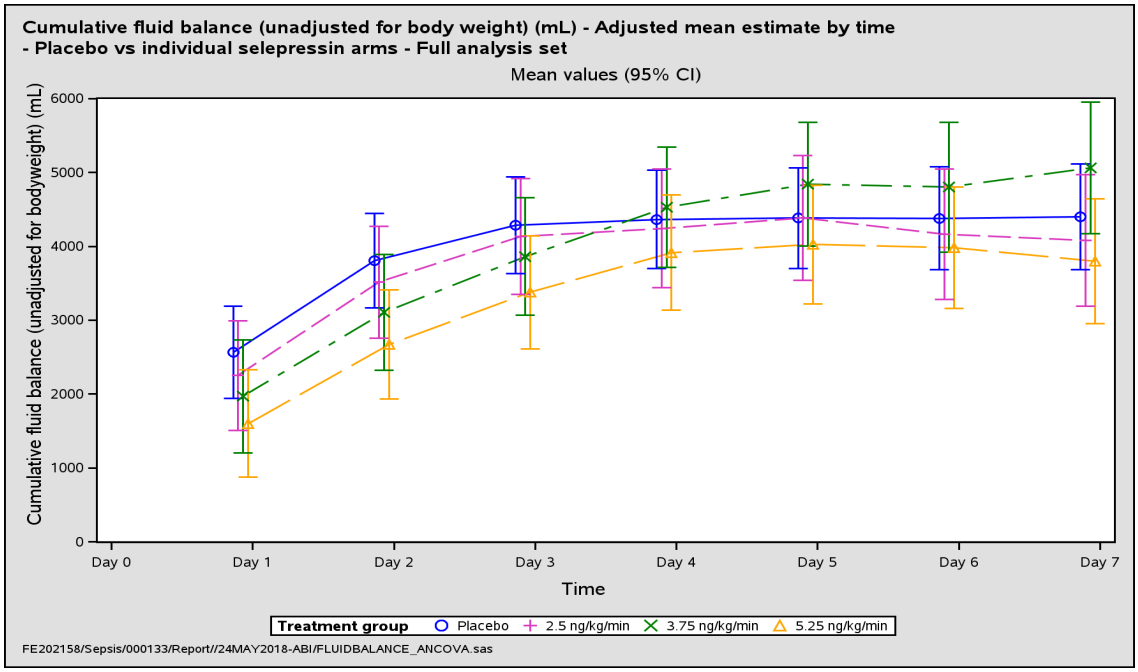


eFigure 13b depicts the relative change in dose of open-label norepinephrine/noradrenaline administered over the first 24 hours after start of the Investigational Medicinal Product (IMP, 'study drug') corrected for the baseline dose of norepinephrine/noradrenaline. Whiskers denote 95% confidence intervals.

eFigure 14. Fluid balance

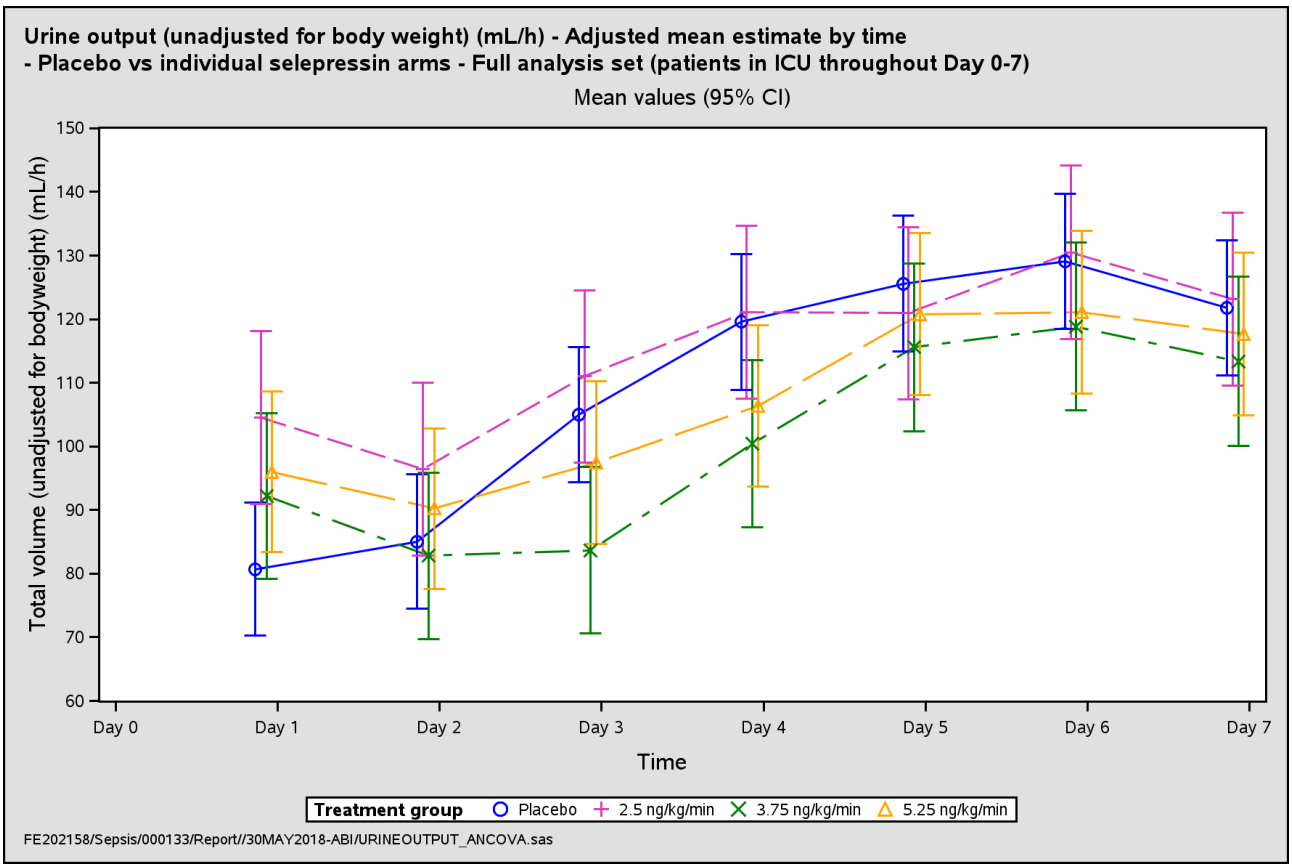


eFigure 14a depicts the daily change in fluid balance from start of the Investigational Medicinal Product (IMP, 'study drug') corrected for the fluid balance from start of sepsis-induced hypotension up to start of the IMP (up to 18 hours). Whiskers denote standard 95% confidence intervals.



eFigure 14b depicts the cumulative fluid balance from start of the Investigational Medicinal Product (IMP, 'study drug') corrected for the fluid balance from start of sepsis-induced hypotension up to start of the IMP (up to 18 hours). Whiskers denote standard 95% confidence intervals.

eFigure 15. Daily urine output



eFigure 15 depicts the daily urine output from start of the investigational medicine product (IMP, 'study drug') corrected for the urine output balance from start of vasopressor therapy to start of the IMP. Whiskers denote standard 95% confidence intervals.

Supplementary tables

eTable 1. Demographics and baseline characteristics by treatment group

Characteristic	Selepressin			Placebo
	2.25ng (n=191)	3.75ng (n=177)	5.25ng (n=194)	(n=266)
Demographics				
Age (years)	67[59;75]	69.0 [62;74]	69 [60;75]	67 [58;77]
Sex (male)	111 (58.1)	107 (60.5)	107 (60.5)	145 (54.5)
Medical patients	204 (76.7)	131 (74.0)	130 (67.0)	204 (76.7)
Weight (kg)	75.0 [64.0;90.5]	77.0 [64.0;90.4]	76.3 [65.0;92.8]	76.6 [63.0;90.0]
Body mass index ($kg/m^{2)}$	26.2 [22.5;31.1]	26.9 [22.7;31.6]	26.2 [23.4;31.6]	26.2 [22.5;31.1]
Severity scores				
Modified SOFA (No CNS)	9.0 [8.0;11.0]	9.0 [8.0;11.0]	9.0 [8.0;11.0]	9.0 [8.0;11.0]
APACHE II	24.0 [19.0;29.0]	26.0 [21.0;31.0]	25.0 [20.0;32.5]	25.0 [21.0;31.0]
Physiological and laboratory values				
Heart rate (beats per minute)	104 [87;119]	102 [87;119]	99 [84;113]	100 [86;116]
Systolic blood pressure (mmHg)	105 [93;117]	102 [92;113]	104 [95;116]	103 [94;115]
Diastolic blood pressure (mmHg)	54 [50;62]	54 [49;60]	54 [49;59]	52 [48;58]
Mean arterial pressure (mmHg)	70.0 [66.0;78.0]	70.0 [64.0;76.0]	70.0 [65.0;76.0]	68.5 [64.0;76.0]
Central venous pressure (mmHg)	11 [8;16]	11 [6;15]	12 [8;15]	10 [8;13]
Respiratory rate (breaths per minute)	22 [19;28]	23 [19;28]	20 [17;25]	22 [18;27]
Albumin (g/L)	22.0 [17.4;26.0]	22.0 [17.4;26.0]	23.0 [19.0;27.0]	23.0 [19.0;26.6]
Creatinine (µmol/L)	140 [97;228]	154 [97;245]	151 [97;245]	159 [101;238]
C reactive protein (mg/L)	222 [114;304]	242 [155;318]	193 [99;280]	208 [106;317]
International normalized ratio	1.45 [1.20;1.80]	1.45 [1.20;1.80]	1.42 [1.27;1.80]	1.43 [1.25;1.78]
Lactate (mmol/L)	2.90 [1.6;4.8]	2.8 [1.6;4.8]	2.4[1.6;3.7]	2.6 [1.7;4.2]
Leukocytes (10^9 cells/L)	13.4 [6.1;21.4]	13.4 [6.1;21.4]	15.2 [6.4;23.0]	13.4 [6.1;21.4]
Hemoglobin (g/dL)	10.9 [9.3;12.0]	11.3 [9.6;12.9]	11.0 [9.4;12.8]	10.7 [9.1;12.1]
Platelets (10^9 cells/L)	184 [101;267]	184 [101;265]	170 [117;251]	181 [104;284]
PaO2/FiO2 ratio (mmHg)	195 [122;310]	201 [120;289]	209[145;301]	205 [128;316]
Concomitant therapy at baseline				
Dose of norepinephrine (µg/kg/min)	0.25 [0.13;0.50]	0.28 [0.15;0.45]	0.25 [0.14;0.43]	0.26 [0.15;0.44]
Total catecholamine dose (µg/kg/min)	0.25 [0.13;0.51]	0.29 [0.15;0.45]	0.25 [0.14;0.45]	0.26 [0.15;0.45]
Dose of norepinephrine ≥ 30 µg/min	74 (39)	72 (41)	63 (32)	98 (37)
On mechanical ventilation (%)	124 (65)	116 (66)	125 (64)	164 (62)
On renal replacement therapy (%)	61 (32)	72 (41)	79 (41)	99 (37)
Site of primary infection				
Lower respiratory tract	75 (39)	74 (42)	73 (38)	99 (37)
Intraabdominal	63 (24)	46 (26)	60 (31)	63 (24)
Urinary tract	51 (19)	26 (15)	26 (15)	51 (19)
Skin/soft tissue	26 (15)	21 (12)	11 (6)	26 (15)
Other	22 (12)	10 (6)	22 (11)	31 (12)
Pre-existing conditions				
Cancer	35 (18.3)	25 (14.1)	34 (17.5)	35 (13.2)
Cardiovascular	90 (47.1)	103 (58.2)	96 (49.5)	132 (49.6)
COPD	41 (15.4)	34 (19.2)	41 (21.1)	41 (15.4)
Diabetes mellitus	47 (24.6)	43 (24.3)	49 (25.3)	67 (25.2)
Liver cirrhosis	13 (6.8)	10 (5.6)	20 (10.3)	23 (8.6)
Kidney disease	23 (12.0)	30 (16.9)	40 (20.6)	41 (15.4)
Charlson co-morbidity index	2.0 [1.0;3.0]	2.0[1.0;3.0]	2.0 [1.0;4.0]	2.0 [1.0;3.0]

Proportions denote number of patients (%), values denote means with ± denoting SD and square brackets denoting 95% confidence intervals. Sequential Organ Failure Assessment (SOFA) was not conducted for central nervous system (CNS) component of the score. Chronic Obstructive Pulmonary Disease (COPD). Pulmonary arterial oxygen pressure / fraction of inspired oxygen (PaO_2/FiO_2) in mmHg. Proportions denote number of patients (%), values denote medians [interquartile range].

eTable 2. Major endpoints by treatment arm

Efficacy endpoints	Selepressin			Placebo
	2.5ng/kg/min (N=191)	3.75ng/min/kg (N=177)	5.25ng/min/kg (N=194)	(N=266)
Primary endpoint - ventilator and vasopressor free days to day 30	14.7 ± 13.1	13.7 ± 12.9	14.2 ± 13.2	14.2 ± 13.1
Pre-specified key secondary endpoints				
Day 90 mortality - number (%)	75 (40.3)	71 (41.3)	81 (43.3)	109 (41.1)
Renal replacement therapy free days * to day 30	18.2 ± 14.4	17.9 ± 14.2	17.9 ± 14.3	18.4 ± 13.9
Intensive care unit free days * to day 30	12.4 ± 12.2	11.59 ± 11.7	11.38 ± 11.9	11.7 ± 11.6
Other mortality endpoints - no. (%)				
Day 30 mortality - number (%)	66 (35.3)	62 (35.2)	62 (35.2)	193 (35.0)
Day 180 mortality - number (%)	75 (40.3)	71 (41.3)	81 (43.3)	109 (41.1)
Other free day endpoints *				
Vasopressor free days to day 30	16.8 ± 13.4	16.2 ± 13.3	16.5 ± 13.3	17.0 ± 13.1
Ventilator free days to day 30	15.3 ± 13.6	14.5 ± 13.4	14.8 ± 13.6	15.0 ± 13.4
Hospital free days to day 90	30.6 ± 33.3	30.2 ± 32.8	28.8 ± 33.1	29.21 ± 32.6
Duration of therapy - days				
Vasopressor to day 30	2.8 ± 3.6	3.7 ± 5.0	3.0 ± 3.9	3.4 ± 3.7
Mechanical ventilation to day 30	5.5 ± 7.8	6.5 ± 8.5	5.8 ± 8.2	6.1 ± 8.1
Renal replacement therapy to day 90	1.7 ± 5.6	1.9 ± 6.0	2.5 ± 10.1	1.6 ± 5.5
Intensive care unit length of stay to day 30	9.1 ± 8.8	10.0 ± 9.1	9.8 ± 9.3	10.3 ± 9.0
Hospital length of stay to day 90	24.5 ± 24.2	26.0 ± 24.4	25.7 ± 23.5	26.5 ± 24.1
Quality of life at day 180 in survivors only				
By visual analogue scale †	24.5 ± 24.2	26.0 ± 24.4	25.7 ± 23.5	26.5 ± 24.1
EQ-5D 5L index score ◊	0.76 ± 0.20	0.74 ± 0.20	0.74 ± 0.24	0.76 ± 0.22

Proportions denote number of patients (%), values denote means with ± denoting SD.

* "Free days" reflects the time from end of last use of therapy to end of the period (30 or 90 days), higher number of days indicating longer period free of therapy. Patients dying in the period are assigned 0 free days.

† The visual analogue score is a patient reported outcome with 100 representing the best thinkable health and 0 representing the worst thinkable health status. 78% and 80% of patients alive in the trial for selepressin and placebo, respectively, completed the questionnaire.

◊ The EQ-5D 5L index score reflects the patient reported level of physical and mental well-being. 80% and 82% of patients alive in the trial for selepressin and placebo, respectively, completed the questionnaire.

eTable 3. Organ dysfunction and organ failure at day 7 and day 30

	Organ dysfunction (SOFA increase ≥1)				Organ failure (increase from ≤2 to >2)			
	Placebo	Selepressin	OR (CI 95%)*	p-value*	Placebo	Selepressin	OR (CI95%)	p-value*
Cardiovascular								
Day 7	1.5%	2.2%	1.37 (0.43-4.38)	0.60	NA	NA	-	-
Day 30	1.5%	3.1%	1.90 (0.62-5.84)	0.26	NA	NA	-	-
Coagulation								
Day 7	51.1%	58.3%	1.45 (1.05-1.98)	0.02	22.7%	33.2%	1.23 (0.86-1.75)	0.26
Day 30	58.3%	63.9%	1.30 (0.94-1.79)	0.10	34.1%	36.2%	1.08 (0.79-1.49)	0.63
Liver								
Day 7	33.6%	35.5%	1.18 (0.85-1.64)	0.32	17.6%	20.5%	1.34 (0.90-2.00)	0.15
Day 30	46.2%	46.4%	1.07 (0.78-1.46)	0.66	32.1%	33.3%	1.12 (0.81-1.56)	0.50
Renal								
Day 7	32.2%	35.3%	1.16 (0.84-1.61)	0.36	19.3%	23.4%	1.23 (0.88-1.85)	0.21
Day 30	42.8%	44.1%	1.05 (0.77-1.43)	0.75	30.7%	33.2%	1.07 (0.77-1.48)	0.68
Respiratory								
Day 7	38.8%	31.7%	0.71 (0.52-0.98)	0.04	19.6%	15.9%	0.76 (0.52-1.13)	0.17
Day 30	45.8%	40.1%	0.78 (0.58-1.06)	0.11	24.2%	20.2%	0.77 (0.57-1.10)	0.14

The proportion of patients developing organ dysfunction (defined as an increase of the respective sequential organ failure assessment (SOFA) score) and organ failure (defined as an increase from a SOFA score of ≤2 to a SOFA score or > 2) after start of the investigational medicine product (IMP). The neurological component of the SOFA score was not registered due to the majority of patients receiving sedation. Note placebo is listed first, contrary to other tables, to facilitate interpretation of odds ratios. *Odds Ratio and p-values are calculated using estimates corrected for baseline values.