Rationale and protocol for the efficacy, safety and tolerability of nangibotide in patients with septic shock (ASTONISH) phase IIb randomised controlled trial

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ABSTRACT

Introduction Septic shock is the subgroup of patients with sepsis, which presents as vasopressor dependence, an elevated blood lactate concentration and is associated with a mortality of at least 30%. Expression of the triggering receptor expressed on myeloid cells 1 (TREM-1) pathway, measured using a serum biomarker of pathway activation (soluble TREM-1, sTREM-1) has been associated with outcome in septic shock. Preclinical and early phase patient data suggest that therapeutic modulation of this pathway may improve survival.

Methods and analysis Efficacy, Safety and Tolerance of Nangibotide in Patients with Septic Shock is a phase IIb randomised controlled trial that will take place in up to 50 centres in seven countries and recruit 450 patients with septic shock to receive either placebo or one of two doses of nangibotide, a novel regulator of the TREM-1 pathway. The primary outcome will be the impact of nangibotide therapy on the change in Sequential Organ Failure Assessment score from a baseline determined before initiation of study drug therapy. This will be assessed first in the patients with an elevated sTREM-1 level and then in the study population as a whole. In addition to safety, secondary outcomes of the study will include efficacy of nangibotide in relation to sTREM-1 levels in terms of organ function, mortality and long-term morbidity. This study will also facilitate the development of a novel platform for the measurement of sTREM-1 at the point of care.

Ethics and dissemination The study has been approved by the responsible ethics committees/institutional review boards in all study countries: Belgium: Universiteit Ziekenhuis Antwerpen, France: CPP Ile de France II, Denmark: Region Hovedstaden, Spain: ethics committee from ValldHebron Hospital, Barcelona, Finland: Tukia, Ireland: St. James’ Hospital (SJH) / Tallaght University Hospital (TUH) Joint Research Ethics Committee, USA: Lifespan, Providence Trial registration numbers EudraCT Number: 2018-004827-36 and NCT04055909.

INTRODUCTION

Sepsis is defined as a life-threatening condition arising as a result of the body’s dysregulated host response to infection. Septic shock is present in the subgroup of patients with sepsis, persistent hypotension requiring vasopressor support and an elevated serum lactate. This multisystem disorder is associated with a 30% mortality and substantial morbidity including a higher risk of mortality during succeeding years, as well as cognitive and physical complications, immune dysfunction, secondary infections, persistent organ damage, impaired quality of life and depression or post-traumatic stress.

The current recommendations for treatment of septic shock remain largely supportive in spite of extensive efforts to develop new therapies. Novel therapeutic approaches that have shown promise in
preclinical development have repeatedly failed in clinical trial. This has led to recognition that conventional randomised controlled trial designs in sepsis may be inadequate for the development of new therapies and that new trial designs that target specific populations within the septic shock population are required.

The triggering receptor expressed on myeloid cells 1 (TREM-1) is an immunomodulatory receptor expressed on innate immune cells, endothelial cells and platelets. The biological function of TREM-1 is the amplification of the inflammatory response. In sepsis, this may contribute to the dysregulated immune response, which plays a role in the development and progression of septic shock. Exaggerated activation of this pathway, measured by high circulating levels of expression of the cleaved portion of the receptor soluble TREM-1 (sTREM-1), is associated with increased mortality in patients with septic shock.

Nangibotide is a 12 amino-acid peptidic fragment derived from TREM-like transcript-1, a receptor protein belonging to the TREM-1 family. Nangibotide can bind the TREM-1 ligand and thereby modulate the amplification of the immune response caused by the activation of the TREM-1 pathway in sepsis.

Extensive preclinical modelling in rodent, porcine and primate septic shock revealed a protective effect of nangibotide in terms of organ function, cardiovascular status and survival. A recent phase IIa clinical trial investigated the safety and tolerability of three doses of nangibotide for up to 5 days in 49 patients with septic shock. In this trial, treatment with nangibotide was found to be safe and well tolerated. Although this study was not designed to prove efficacy, nangibotide treated patients demonstrated numerical improvements in markers of organ function consistent with the hypothesis that TREM-1 inhibition may improve outcomes in septic shock patients. This effect was larger in the subgroup of patients with high circulating levels of sTREM-1.

We report the clinical and statistical design of the Efficacy, Safety and Tolerability of Nangibotide in Patients with Septic Shock (ASTONISH), a randomised, double-blind, placebo-controlled dose selection phase IIb study in patients with septic shock. The study includes a number of innovative components to address the limitations of previous studies in this area and a novel analytical approach to determining the primary outcome.

**METHODS AND ANALYSIS**

**Objectives**

**Primary**

- To evaluate the efficacy of two doses of nangibotide on organ dysfunction (Sequential Organ Failure Assessment, SOFA score) in patients with septic shock in relation to their sTREM-1 plasma levels (patients with high sTREM-1 levels at baseline and all patients).

**Secondary**

Secondary objectives of the study are to investigate the safety and efficacy of two doses of nangibotide in patients with septic shock in relation to their sTREM-1 levels.

This includes:

- To evaluate the effect of nangibotide on mortality for up to 12 months.
- To evaluate the effect of nangibotide on other clinical parameters (eg, duration of shock, vasopressor use, ventilator and renal replacement use, secondary infections).
- To evaluate the safety and tolerability of nangibotide.
- To evaluate the effect of nangibotide on quality of life, resource utilisation and postshock morbidity.

**Box 1 Inclusion and exclusion criteria for the Efficacy, Safety and Tolerability of Nangibotide in Patients with Septic Shock study**

**Inclusion criteria**

- Provide written informed consent (proxy/legal representative) according to local regulations.
- Age 18–85 years (inclusive).
- Documented or suspected infection: lung, abdominal, in patients aged ≥65 years, urinary tract infection.
- Organ dysfunction defined as acute change in total Sequential Organ Failure Assessment score ≥2 points.
- Refractory hypotension requiring vasopressors to maintain MAP ≥65 mm Hg despite adequate volume resuscitation (as per recommendations of the Surviving Sepsis Campaign).
- Hyperlactataemia (blood lactate >2 mmol/L or 18 mg/dL). This criterion must be met at least once for the purpose of diagnosis within the 24 hours before study drug administration.

**Exclusion criteria**

- Previous episode of septic shock requiring vasopressor administration within current hospital stay.
- Underlying concurrent immunodepression with anti-CD52 alemtuzumab or glucocorticoids >75 mg prednisone daily or equivalent for more than 7 days.
- Immunosuppressive therapy related to recent (<6 months) transplantation.
- Cancer chemotherapy (<3 months) implying an immunodepression.
- Known HIV infection with low CD4 cell count (<200) for at least 6 months.
- Known pregnancy (positive urine or serum pregnancy test).
- Shock of any other cause.
- Ongoing documented or suspected endocarditis, history of prosthetic heart valves.
- Prolonged QT syndrome.
- End-stage neurological disease.
- End-stage cirrhosis (Child Pugh Class C).
- Acute Physiology and Chronic Health Evaluation score <15 or ≥34.
- Home oxygen therapy on a regular basis for >6 hours/day.
- Recent cardiopulmonary resuscitation (within current hospital stay).
- Body mass index ≥40 kg/m² or weight ≥130 kg.
- Moribund patients.
- Decision to limit full care taken before obtaining informed consent.
- Participation in another interventional study in the 3 months prior to randomisation.
Exploratory
► To evaluate PK/PD relationship to nangibotide-mechanism-of-action-related markers.

ASTONISH trial design
This is a multicentre randomised, double-blind, placebo-controlled dose-selection study in which two doses of nangibotide will be tested versus placebo. It will take place in approximately 50 centres in seven countries: France, Belgium, Denmark, Finland, Spain, Ireland and the USA. The study was initiated in November 2019. Additional sites may be added depending on recruitment rate.

Eligibility
All patients with a diagnosis of septic shock will be considered for study participation. The applicable local requirements for informed consent will be followed. All patients will receive standard of care for the treatment of septic shock.

After screening for eligibility by a central coordinating centre, patients meeting the inclusion and exclusion criterion will be consented by the site team and randomised (box 1).

Study drug
All patients will be treated with standard therapy for septic shock. In addition, patients will receive a loading dose of nangibotide over fifteen minutes followed by infusion at one of two doses (6.66 mg/kg+0.3 mg/kg/hour or 20 mg/kg+1.0 mg/kg/hour) or a matched placebo.

Treatment with study drug must be initiated as early as possible, but no later than 24 hours after the onset of septic shock, defined by the start of vasopressor therapy. Blood samples for pharmacokinetic and exploratory pharmacodynamic analyses will be collected before, during and after the treatment period.

Patients will be treated for at least 3 days (72±2 hours) with study drug or until 24 (±2) hours after vasopressor withdrawal with a maximum treatment duration of 5 days (120±2 hours) (figure 1).

Blinding
ASTONISH is a double-blind trial. Study personnel including investigators, patients, sponsor and contracted research organisations will be blinded to treatment allocation until closure of the primary endpoint data set at day 28. Unblinding will only take place if knowledge of the patient treatment allocation would facilitate emergency treatment. The investigational drug and the placebo are indistinguishable and presented in the same way.

Endpoints
Primary endpoint:
The primary endpoint is the change of total SOFA score from baseline to day 5, which will be assessed in the subgroup defined by patients with elevated sTREM-1 baseline levels (≥400 pg/mL) and in the overall population.

Prespecified secondary endpoints will include:
Efficacy parameters:
Key secondary endpoint.
► All-cause mortality on day 28.
Secondary endpoints.
► Duration of Intensive Care Unit (ICU) stay, hospitalisation.
► Organ support-free survival.
► Daily change of total SOFA score and subscores
► Time until shock reversal defined as cessation of vasopressor support for 24 hours
► Vasopressor use.
► Invasive mechanical ventilation.
► Renal support.
► Overall survival at 90 days, 6 and 12 months.
► Septic shock-related mortality up to 90 days, 6 and 12 months.
► Incidence of secondary infections and postshock antibiotic use.
Safety parameters:
► Vital signs.
► ECG.
► Safety laboratory tests: haematology, coagulation, plasma biochemistry.
► Presence of antinangibotide antibodies.
► AEs, SAEs and deaths.

Pharmacokinetics:
Nangibotide plasma levels
Pharmacodynamics (exploratory): sTREM-1, immune and vascular-related biomarkers.
Pharmacoeconomic endpoints up to 12 months:
► Health-related quality of life (EQ-5D).
► Postshock morbidity.
► Healthcare resource utilisation.

Figure 1 Study flow chart. CCC, Central Co-ordinating centre; EoS, end of study; Fu, follow-up; LD, loading dose or matching placebo.
Patients will be assessed at the End of Study visit at day 28. After the last patient’s day 28 visit, the study data will be analysed. Additional follow-up (FU) visits will be conducted after 90 days, 6 and 12 months. Quality of life, morbidity and survival status of patients will be collected at these visits which may be undertaken remotely in order to minimise loss of patients to FU. Data from the long-term FU will be analysed and reported separately (a complete list of study investigations and their timing is presented in online supplemental files 1 and 2). Adverse event (AE) data will be collected until day 28, drug-related serious AEs (SAEs) can be reported without time limit.

sTREM-1 is a mechanism-based plasma marker associated with activation of the TREM-1 signalling pathway. As such it may be a biomarker predictive of treatment response to nangibotide. The plasma levels of sTREM-1 will be determined at the second interim analysis and at the end of the study for the biostatistical analysis.

**Randomisation and sample size**

Following screening for eligibility, study centres will contact a central, independent coordinating centre to confirm eligibility. They will then be issued with a unique randomisation code that will facilitate identification of the correct blinded allocation of study drug.

The randomisation will be stratified according to site and patients will be allocated on a 1:1:1 basis to one of three treatment arms. The randomisation scheme will be generated by an independent statistician who is not part of the study team. A randomisation number will be assigned to each patient. The randomisation assignment will be implemented by an interactive response technology.

Results from a previous pilot phase II study (MOT-C-201) have shown that a difference of around two versus placebo in mean changes of the primary endpoint (accounting for missing values occurring prior to day 5) and an SD of around 3.3, could be expected in the overall population, and even higher than two in the subgroup of patients with elevated sTREM-1 levels. It is expected that the high sTREM-1 subgroup will comprise at least half the patients enrolled (around 225 patients) in the study.

Considering 450 patients (150 patients per treatment arm), this study has at least 90% power to detect the expected difference in at least one dose either in the subgroup of patients with elevated sTREM-1 levels or in the overall population.

**Analysis plan**

This exploratory study has three parallel aims

- Assessment of the safety and tolerability of two doses of nangibotide.
- Assessment of the efficacy of two doses of nangibotide on the primary and secondary efficacy endpoints.
- Determining the best cut-off for baseline sTREM1 as a predictive biomarker.

The primary efficacy variable is the change of SOFA from baseline to day 5. This will be tested in the subgroup defined by patients with elevated sTREM-1 baseline levels and in the overall population. This will be based on an analysis of covariance model adjusting for randomised treatment and the baseline SOFA score.

The primary analysis will be undertaken in the modified intention to treat set (all randomised patients having received at least one dose of the prescription of study drug (either nangibotide or placebo).

Missing values occurring prior to day 5 are likely to be missing not at random and will be replaced as follows:

- Missing SOFA values not due to death will be replaced by the last available postrandomisation value of the SOFA score (ie, last observation carried forward method).
- Missing values due to death will be replaced by the last available postrandomisation value of the total SOFA score increased by an additional penalty of four points.

Sensitivity analyses using different penalty scores and other methods for handling missing data will be performed and described in the Statistical Analysis Plan (SAP).

This is a phase IIb trial, therefore, no adjustment for multiplicity will be proposed for the primary analysis and tests for nangibotide doses versus placebo comparisons will be performed at the usual nominal one-sided alpha level of 0.025 both in the subgroup and the overall population. However, a secondary adjusted analysis will be performed to account for multiplicity and control the overall one-sided error rate to 0.025: details will be further provided in the SAP before the unblinding of the database.

The key secondary endpoint of 28-day mortality will be assessed using a log-rank test to compare the treatment arms. In addition, a proportional hazard Cox model adjusting for the same covariates used for the primary endpoint analysis will be fitted to estimate the treatment effect.

Details of other endpoint analyses are described in the SAP.

The threshold for categorising high and low sTREM-1 is defined as 400 pg/mL at baseline and is based on analysis of biomarker and outcome data from the phase IIa study. However, exploratory analyses based on the current study will be conducted to confirm the optimal cut-off for future studies.

After the first 113 (around 25%) and 225 (50%) patients have completed the 7-day period after randomisation, unblinded interim analyses of safety will be performed and the data reviewed by an independent data monitoring committee (DMC). The second interim analysis will, in addition, include an analysis of efficacy data, after which the DMC will make recommendations for stopping the clinical trial or a treatment arm for futility (see online supplemental file 3 for DMC Charter). As well, if the proportion of patients with high sTREM-1 baseline values is less than 50% of the total, then the planned total sample size may be increased to maintain the power of the subgroup analyses. Data will be validated using on
site visits and source data verification by blinded clinical research associates.

PATIENT AND PUBLIC INVOLVEMENT
No patient involved.

Ethics and dissemination
Ethical approval has been secured in Belgium, France, Denmark, Finland, Ireland and Spain in Europe and in the USA.

Consent for this study cannot be secured from a substantial proportion of eligible study participants due to lack of capacity associated with their diagnosis of septic shock. An emergency informed consent procedure will be applied according to applicable regulations and to the approval of the respective ethics committee or institutional review board in patients who are assessed by their treating clinician as lacking capacity. Consent for further data/sample collection may be withdrawn by the patient at any time after they have regained capacity (an example consent form is provided in online supplemental file 4).

A manuscript with the results of the primary study will be published in a peer-reviewed journal and anonymised throughout. Separate manuscripts may be written on the secondary aims, and these will also be submitted for publication in peer-reviewed journals. Results will also be disseminated at national and international meetings (see online supplemental file 5) for Standard Protocol Items: Recommendations for Interventional Trials checklist).

DISCUSSION
This study has several novel components in terms of study design and analysis.

Nangibotide is the first compound to reach clinical trial that targets the critical TREM-1 pathway. This study will explore the efficacy of nangibotide in septic shock patients with elevated baseline levels of sTREM-1, a biomarker that reflects excessive activation of the target pathway and is associated with increased mortality. This approach may provide evidence for the design of a future phase III trial utilising a personalised, mechanism based biomarker to select patients likely to benefit from nangibotide.

In addition to selecting patients based on the clinical presentation of septic shock, this study employs additional prognostic enrichment by excluding those patients with Acute Physiology and Chronic Health Evaluation scores less than 15 or greater than or equal to 34 at baseline. This approach excludes patients at a low risk of death and those with a high estimated mortality (≥85%) for whom nangibotide treatment is unlikely to be of benefit, reduces the outcome heterogeneity within the septic shock population and increases the likelihood of detecting a clinically relevant benefit.

The statistical analysis plan for this study includes the analysis of the primary endpoint in both the whole study population and the subgroup of patients with high sTREM-1 levels. This proposed stepwise analytical approach will offer adequate power to detect the efficacy of nangibotide in both patient groups while preserving confidence that a false positive result is unlikely.

The challenge of detecting clinically relevant benefit in phase II studies of novel therapeutic agents in septic shock is a substantial one which has been recognised by the clinical community and regulators. Change in SOFA, an established marker of the acute morbidity associated with sepsis, has been consistently shown to act as a surrogate for subsequent mortality in septic shock. By incorporating robust guidelines for collection of clinical information and the handling of missing data, this study may improve the consistency and handling of data of this kind in randomised controlled trials.

Limitations of this phase Ib study include the use of a surrogate endpoint to detect clinically relevant efficacy. While the change in SOFA score has been extensively validated, further studies will be required to demonstrate improved mortality as a primary outcome. Furthermore, by defining a priori the subgroup of patients with elevated sTREM-1 levels as those most likely to benefit, the available statistical power to detect a benefit only in those patients with low sTREM-1 levels at baseline is reduced.

Specific treatments for septic shock have remained elusive and given the increasing prevalence, substantial mortality and morbidity that is associated with it, the demand for novel therapies to treat the condition continues to be high. With increasing recognition that a variety of endotypes exist within the population characterised by the standard definitions, novel agents targeting subgroups most likely to benefit from treatment offer an attractive approach. Nangibotide is the first agent to target the TREM-1 pathway in patients, and the ASTONISH trial will provide valuable insights into both the safety and efficacy of this novel therapy in the treatment of patients with septic shock.
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REFERENCES
Efficacy, Safety and Tolerability of Nangibotide in Patients with Septic Shock.

A Randomized, Double-blind, Placebo Controlled Dose Selection Study

The ASTONISH Study (MOT-C-203)

Table 1: Study Schedule

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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK¹⁰</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biomarker samples (see table 2)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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</tr>
<tr>
<td>EuroQol (EQ 5D)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthcare resource utilization⁶</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary infections⁸</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge letter collection¹⁰</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

SCR: screening; EoS: end of study; FU: Follow-up; CCC: Clinical coordination center; d: day; w: week; m: month

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2021; BMJ Open, et al. Francois B

Supplemental material
1: Study days refer to calendar days, day 0 is defined as the calendar day of first study drug administration
2: By phone only
3: All medication taken within the last 24 hours before start of treatment should be documented
4: Women of childbearing potential
5: Estimate in case measurement is not feasible
6: Daily up to day 7, even in case of intensive care unit (ICU) discharge
7: Patients will be treated for at least 3 days (72 ±2 hours) with study drug. After the first 3 days of treatment, patients still requiring vasopressor will be treated until 24 (±2) hours after vasopressor withdrawal with a maximum treatment duration of 5 days (120 ±2 hours)
8: Day 28 completed at site (including duration of hospitalization and ICU stay, discharge location); 90 days, 6 and 12 months via phone call
9: Day 28 completed by site
10: Discharge letters from ICU discharge, hospital discharge and for every hospitalization starting before day 28 (where permissible)
11: In case of emergency consent, confirmation of consent as soon as patient is capable
12: Before first treatment administration
13: Daily until end of infusion
14: Brief physical examination
15: In triplicate, at least 1 minute apart
16: AEs will be collected until day 28 as specified in section
17: For sites where it is not technically feasible, the collection of PK samples may be waived by the sponsor
<table>
<thead>
<tr>
<th>Test</th>
<th>Parameters</th>
<th>Timepoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory assessments for SOFA¹</td>
<td>Bilirubin, platelets, creatinine, arterial blood gases</td>
<td>Daily until D7</td>
</tr>
<tr>
<td>Chemistry¹</td>
<td>Aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase,</td>
<td>Screening, baseline (D0), D1 to D5, D28 from routine laboratory assessments, first routine sample of the day</td>
</tr>
<tr>
<td></td>
<td>total bilirubin, creatinine, urea, glucose, sodium, potassium, chloride,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>calcium, inorganic phosphate, total protein, albumin, lactate</td>
<td></td>
</tr>
<tr>
<td>Hematology¹</td>
<td>Hemoglobin, hematocrit, leucocytes, basophils, eosinophils, neutrophils,</td>
<td>Screening, baseline (D0), D1 to D5, D28 from routine laboratory assessments, first routine sample of the day</td>
</tr>
<tr>
<td></td>
<td>lymphocytes, monocytes, platelet count</td>
<td></td>
</tr>
<tr>
<td>Coagulation¹</td>
<td>International Normalized Ratio (INR)</td>
<td>Screening, baseline (D0), D1 to D5, D28 from routine laboratory assessments, first routine sample of the day</td>
</tr>
<tr>
<td>Anti-drug antibodies²</td>
<td>Anti-drug antibodies</td>
<td>Baseline (pre-dose) and D28</td>
</tr>
<tr>
<td>Cytokines, markers of vascular</td>
<td>TNFα, IL-6, IL-10, CCL2 (MCP-1), procalcitonin, Ang-1, Ang-2</td>
<td>Baseline (pre-dose), D1 to D5: daily</td>
</tr>
<tr>
<td>endothelium activation²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK</td>
<td>Nangibotide circulating levels</td>
<td>Baseline (pre-dose), D1 to D5: daily until end of infusion Within 3h after the end of the IMP infusion (if possible)</td>
</tr>
<tr>
<td>sTREM-1 RUO/IUO²</td>
<td>soluble TREM-1</td>
<td>Baseline (pre-dose), D1 to D7: daily, D28</td>
</tr>
<tr>
<td>Blood samples for retention</td>
<td>Exploratory biomarkers</td>
<td>Baseline (pre-dose), D1 to D5: daily</td>
</tr>
<tr>
<td></td>
<td>Exploratory transcriptomic biomarkers (PAXgene RNA)</td>
<td>Baseline (pre-dose), D2, D5 and D28</td>
</tr>
</tbody>
</table>

1: Site; 2: Centralized, third party laboratory provider; RUO: research use only; IUO: Investigational Use Only; ICU: Intensive Care Unit
DATA MONITORING COMMITTEE (DMC) CHARTER

MOT-C-203

Efficacy, Safety and Tolerability of Nangibotide in Patients with Septic Shock.
A Randomized, Double-blind, Placebo Controlled Dose Selection Study

Test Product: Nangibotide
Sponsor: INOTREM S.A.
114 Rue La Boétie
75008 Paris
France
Sponsor’s Medical Officer: Jean-Jacques Garaud, MD
Sponsor Protocol Number: MOT-C-203
EudraCT Number: 2018-004827-36
pIND: 131824
Development Phase: IIb

DMC Chair: Michel Wolff, MD
Version: 2.0
Date: 10 October 2019

Confidential

Information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical/regulatory review of the study, without written authorisation from INOTREM SA or its affiliates.
5 PREAMBLE

An independent data monitoring committee (DMC) will be appointed to guide dose selection and to monitor the safety of study MOT-C-203 “Efficacy, Safety and Tolerability of Nangibotide in Patients with Septic Shock: A Randomized, Double-blind, Placebo Controlled Dose Selection Study”

6 MEMBERS

The DMC will comprise experts with experience in the treatment of sepsis and septic shock and the conduct of clinical trials in this indication. It will consist of 4 members including 3 specialists in intensive care medicine and management of patients with septic shock, and a methodologist (biostatistician) with experience in the conduct and the safety assessment of clinical trials. All four are voting members. The chair of the DMC will be appointed by the sponsor, INOTREM. Other DMC members and back-ups will be mutually agreed between the sponsor and the DMC chair. The DMC members should be free of financial or scientific conflicts of interest and are responsible for advising the Sponsor of any changes in interests that would affect their objectivity. All DMC members will provide a signed CV and financial disclosure forms to the sponsor prior to the constitution of the DMC.

The current list of members and their contact information is provided in appendix 1.

7 RESPONSIBILITIES

The DMC will be responsible for:

- Reviewing safety data from an unblinded interim analysis after 112 (25%) randomized patients completed day 7
- Reviewing safety and efficacy data from an unblinded interim analysis after 225 (50%) randomized patients completed day 7 and making a recommendation for the study or a treatment arm to stop in case of futility or making a recommendation for the increase of sample size
- Reviewing SAEs and other safety data on an ongoing basis
- Reviewing the general progress of the clinical study with regard to accrual/withdrawals or drop-out rates and clinical study conduct

In addition to the review of unblinded safety data at 25% and safety and efficacy data at 50% of patients treated, DMC members may have access to unblinded safety data for one or more patients where necessary. However, no members of the study team at INOTREM, at the Contract Research Organization (CRO) or the sites will have access to unblinded data until after database lock is declared. In case unblinded data needs to be handled or analyzed before database lock, these tasks will be performed by persons independent from the study team.

8 DMC MEETINGS

8.1 Meeting Schedule

DMC meetings will be held at the following timepoints:

- Initial Meetings for the set-up of the DMC and its procedures (e.g. charter, analysis plans)
- Unblinded meetings for the assessment of interim analyses
- Additional or unscheduled meetings
8.2 Format and Scheduling of Meetings

The preferred meeting format will be face-to-face meetings held at INOTREM's offices in Paris. However, meetings in the format of a teleconference with single or all participants calling by phone may be conducted, depending on the availability of the person. The meeting will consist of an open and a closed part. During the open part, the sponsor will present available data and provide responses to questions. During the subsequent closed part, only the DMC members will discuss the data and decide on recommendations to the sponsor. The closed session discussions are confidential.

The meetings will be scheduled by the DMC chair in cooperation with the sponsor. Effort should be made to keep the timelines between the data lock point and the DMC recommendations as short as possible. The sponsor will communicate the current study status on a regular basis and agree timelines with the DMC for their review in advance.

The content of the DMC briefing packages will be agreed between the sponsor and the DMC chair and may be adjusted during the course of the study. This will be documented in a separate document "DMC Statistical Analysis Plan".

The summary data reports will be provided to the DMC members prior to the scheduled meeting. Due to the nature of the study, these may be available only on a short notice. Efforts will be made to provide these at least 24 hours prior to the meeting. INOTREM will liaise with the DMC chair to ensure availability of the DMC members for review.

8.3 Initial DMC Meetings

The first meetings of the DMC will be organizational meetings. They will be held during the final stage of study set-up, to provide advisory review of the scientific and ethical issues relating to the study design and conduct, to discuss the standard operating procedures for the role and functioning of the DMC, and to discuss the format of reports that will be used to present trial data at future DMC meetings.

8.4 Unblinded DMC Meetings for the Assessment of Interim Analyses

Unblinded DMC meetings for the assessment of interim analyses are scheduled at the following timepoints:

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>25% of patients treated (i.e. 112 patients completing D7)</td>
<td>Safety</td>
</tr>
<tr>
<td>50% of patients treated (i.e. 225 patients completing D7)</td>
<td>Safety; Efficacy: assessing the study or a treatment arm for futility</td>
</tr>
</tbody>
</table>

8.4.1 Interim Assessments of Safety

After the completion of day 7 of the last patient of the respective review point, the sponsor will provide a report with cumulative safety and PK data (as available) for the DMC to review. The «data lockpoints» is defined as day 7 of the last patient for the respective timepoint.
The following data will be required:

<table>
<thead>
<tr>
<th>Data</th>
<th>Description/Format</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Adverse Events</td>
<td>All SAE data as line listing and CIOMS forms (blinded)</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>Tabular report of all adverse events, available in the eCRF system 24 hours after the data lock point. Sites should make effort to complete data entry for safety data for all patients until then.</td>
</tr>
</tbody>
</table>
| Demographics and Vital Signs | • Demographics data listing  
                                 | • Blood Pressure data listing  
                                 | • Body temperature data listing                                      |
| Clinical Laboratory       | Tabular report of the parameters available in the eCRF system:  
                                 | • Chemistry: Aspartate aminotransferase, alanine aminotransferase,  
                                 | alkaline phosphatase, total bilirubin, creatinine, urea, glucose, sodium,  
                                 | potassium, chloride, calcium, inorganic phosphate, total protein,  
                                 | albumin, lactate  
                                 | • Haematology: Hemoglobin, hematocrit, leucocytes, basophils,  
                                 | eosinophils, neutrophils, lymphocytes, monocytes, platelet count  
                                 | • Coagulation: International Normalized Ratio (INR), disseminated intravascular coagulation (DIC) score  
                                 | • Pregnancy test.                                               |
| ECG                       | ECG Data listing                                                                   |
| Patient narratives        | Narratives (discharge letters) of for all patients                                 |
| PK data                   | PK data will be provided to the extent available at the respective datalock point |

Details on the briefing documentation such as tables, listings and figures will be defined in the DMC statistical analysis plan (Appendix 2).

8.4.2 Interim Assessments of Efficacy (Futility)

The interim analysis after 225 patients will also include an assessment of efficacy for deciding on whether one treatment arm or the entire study should be stopped for futility.

The assessment of futility will be made primarily on the basis of the primary endpoint (change in SOFA score). The recommendation should be based on the "standardized effect", which is defined as the difference in LSMEANS (placebo - dose) in the ANCOVA model for the analysis of the primary endpoint divided by the residual standard deviation. Hence a positive standardized effect favors the nangibotide dose and vice versa.

Nevertheless, the clinical endpoint all-cause-mortality after day 28 should also be taken into consideration. The difference in mortality rates (placebo - dose) will also be provided. A positive estimated difference in mortality rates favors the nangibotide dose and vice versa.

Details on the briefing documentation such as tables, listings and figures will be defined in the DMC statistical analysis plan (Appendix 2).

For the assessment of futility, each dose should be assessed separately.
Rules to claim a dose futile are defined below:

- IF the standardized effect is $< +15\%$ in both populations (i.e. all comers and subgroup with high sTREM-1 levels, G2)

AND

- the difference in mortality rates is $< +5\%$ in both populations (i.e. all comers and subgroup with high sTREM-1 levels, G2)

$\rightarrow$ the dose is considered futile

In addition:

If there is a major safety issue with the dose (risk-benefit no longer acceptable), the treatment arm should be considered futile.

A description of the process for deciding on the futility of one dose is provided in Figure 1, a summary of the futility decisions is provided in Figure 2.

---

**Figure 1: Decision Tree for Assessing Futility of a Treatment Arm**

- Both doses futile or unsafe $\rightarrow$ Trial on hold
- One dose non futile and safe $\rightarrow$ Continue study with this dose
- Both doses non futile and safe $\rightarrow$ Continue study with both doses

---

**Figure 2: Decision Tree for Futility Decisions**
For the assessment of futility, it should be taken into account, that the dataset on D28 mortality is limited on sample size and may even be not complete. A decision to stop a treatment arm or the study for futility on grounds of mortality should be confirmed with complete D28 mortality data.

Further details will be defined in the DMC statistical analysis plan (Appendix 2).

8.4.3 Additional DMC Meetings

Additional meetings of the DMC can be scheduled by the DMC chair or the sponsor as deemed necessary for the assessment and discussion of safety aspects.

8.5 DMC Recommendations

The DMC recommendations after each DMC meeting will include one of the following:

- Continuation of the study without modifications
- Continuation of the study with modifications. The recommended modifications may be within or beyond the adaptive feature of the study protocol (study protocol section 8.2).
- Request for additional information
- Suspension of the study (put study “on-hold”) on grounds of safety for consultation with regulatory authorities
- Discontinuation of the study on grounds of safety

For the DMC meeting after 225 patients, the DMC recommendation will include one of the following:

- Discontinuation of study on grounds of futility or safety
- Discontinuation of one treatment arm on grounds of futility or safety

The DMC chair will communicate their recommendation to the sponsor immediately after the end of the closed part of the DMC session orally or by phone followed by an email.

8.6 Meeting Minutes

The DMC will prepare closed minutes of their meeting. The minutes will be signed by all DMC members and originals kept by the Chairperson until unblinding of the study. Following each meeting, summary minutes will be drafted and distributed within 2 business days by the Chairperson to the other DMC members. The minutes will be reviewed and approved by the DMC members within 5 business days of distribution and signed by the chair of the DMC. The Final minutes will be kept securely by the DMC chair and transferred to the sponsor after database lock.

8.7 Records Retention

The DMC Chair will retain copies of all meeting minutes, notes, copies of safety reports and findings, vote results, recommendations and reports used in the evaluation of safety of protocol until database lock is declared by the sponsor, at which time the materials will be transferred to the Sponsor.

9 REPORTING OF STUDY PROGRESS AND IMPORTANT EVENTS TO DMC

The sponsor will report the progress of the study to the DMC members on a regular basis. The following important events will be reported to the DMC immediately:

- Serious Adverse Event with the outcome «death»
10 COMMUNICATION POLICY

It is the responsibility of the Sponsor to communicate with the sites and ethics committees (where required) on a regular basis. The initial communication will include a copy of this charter and previous DMC recommendations.

11 ACCEPTANCE OF DMC RECOMMENDATIONS

It should be understood that the DMC represents an advisory body for the Sponsor. While it is unlikely that the sponsor would ignore DMC recommendations, the company is not obliged to follow DMC recommendations. Thus, upon receiving a DMC recommendation, the Sponsor will decide upon appropriate potential steps in consultation with the DMC, and/or relevant regulatory authorities, as required. It is understood that the Sponsor can elect to continue, interrupt, or close the study even if the DMC were to recommend a different course of action.

If the DMC recommends study interruption/termination, the Sponsor may also request consultation from relevant regulatory authorities.

Once a DMC recommendation to stop the study is accepted, the Sponsor will be responsible for notifying regulatory agencies, investigators, and ethics committees of the DMC’s recommendations and the company’s decision to stop the study. These activities will be performed consistent with GCP guidelines and relevant regulatory requirements.

If the DMC recommends that the trial be stopped, but the Sponsor decides to continue the trial, the Sponsor will provide a written explanation of the decision to the DMC within 14 business days. If a DMC recommendation to stop the study is rejected by the Sponsor, the company will be responsible for notifying regulatory agencies, investigators and ethics committees of the DMC’s recommendations and the company’s decision to continue the study. These activities will be performed consistent with GCP guidelines and relevant regulatory requirements.

The Sponsor or the investigators are at liberty to interrupt or close the study at one or more sites without consulting the DMC. However, it is expected that the DMC would be notified of such actions.
# INFORMATION LETTER TO PARTICIPANTS AND INFORMED CONSENT FORM

<table>
<thead>
<tr>
<th>NAME OF STUDY:</th>
<th>Efficacy, Safety and Tolerability of Nangibotide in Patients with Septic Shock. A Randomized, Double-blind, Placebo Controlled Dose Selection Study The ASTONISH Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>STUDY NUMBER:</td>
<td>MOT-C-203</td>
</tr>
<tr>
<td>EudraCT NUMBER:</td>
<td>2018-004827-36 131824</td>
</tr>
<tr>
<td>STUDY SPONSOR:</td>
<td>Inotrem S.A. 114 Rue La Boétie 75008 Paris France</td>
</tr>
<tr>
<td>STUDY DOCTOR (INVESTIGATOR):</td>
<td>[Investigator Name] [Site Address] [Office Hours Tel] [Out of Hours Tel]</td>
</tr>
<tr>
<td>PATIENT ID NUMBER</td>
<td></td>
</tr>
<tr>
<td>PATIENT FIRSTNAME / LASTNAME</td>
<td></td>
</tr>
</tbody>
</table>

**Information vital to your decision to take part**

This document is intended for patients who are being considered for participation in a research trial. However, if the patient is incapable of providing consent due to the severity of his/her illness, the consent of a relative or other representative will be sought. This procedure was approved by the Ethics Committee of the study and is in line with current laws. At any time during the trial, if the patient becomes capable of providing consent, informed consent will be sought from him/her as a condition of his/her continuing participation.

In this document, “you” always refers to the patient. If you are a patient’s representative, please remember that “you” refers to the patient.
Dear Sir, Dear Madam,

You are being suggested to consider whether you would like to participate in a clinical research study (also called “trial”) to evaluate an investigational medicinal product (also called “drug”) for the treatment of your disease (septic shock). An investigational medicinal product is a drug that is still being studied to evaluate its efficacy, safety and mode of action and is not yet approved by the health authorities. The drug being evaluated in this study is called nangibotide. The following information describes the study and your role as a possible participant. Your participation in this study is entirely voluntary. You do not have to take part, and you may discontinue your involvement at any time without penalty or loss of benefits to which you are otherwise entitled. Please read this information carefully and do not hesitate to ask your study doctor any questions to ensure that you are able to make an informed decision as to whether to participate.

Who is funding this research?
Inotrem S.A. (a pharmaceutical company) will be organizing and funding this study. Inotrem S.A. will compensate your study doctor and/or the study site to cover their costs of conducting this study through a convention. If applicable, your study doctor will disclose to you any financial links or other interests that he/she may have to the sponsor.

What is the purpose of this clinical research study?
The main purpose of this trial is to obtain more information on how efficient and well tolerated nangibotide combined with standard of care is in patients with septic shock compared with standard of care alone.

Sepsis is the result of an overwhelming inflammation response to an acute infection, and it can be life-threatening. Sepsis occurs when the substances released into the bloodstream by your body to fight the infection also harm your body. Anyone can develop sepsis, but the risk is higher in older adults or in patients with weakened immune systems. If sepsis progresses to septic shock, blood pressure drops dramatically, with multiple organs no longer working properly, and may require the use of vasopressors (i.e., a treatment to increase blood pressure) and other treatments to support the failing organs. Septic shock is the cause of death of a great proportion of patients who suffer from it. Surviving patients often experience long-term dysfunctions of their organs and an altered quality of life.

To date, people with septic shock are treated with antibiotics to kill the bacteria responsible for the infection and other supportive treatments and procedures based on symptoms, but no septic shock-specific therapy is currently available.

Study treatment
Nangibotide is an investigational new drug that has been developed by a pharmaceutical company called INOTREM S.A. (the “sponsor”). Nangibotide is a chemically synthesized peptide (small protein) that inhibits the activation of TREM-1, a protein expressed on certain blood cells that is responsible for the overwhelming response of your organism to infection. Nangibotide has the potential to reverse this abnormal inflammatory response that occurs in septic shock. Previous animal experiments showed that nangibotide can control the immune system and diminish the damage linked to septic shock.

The safety and tolerability of nangibotide have been investigated in two previous trials in 21 healthy volunteers and 37 patients with septic shock, who received nangibotide as continuous intravenous infusion. The drug was found to be safe and well tolerated by the volunteers/patients at all tested doses.

The investigational drug nangibotide will be administered in addition to the standard of care for your condition. Standard of care for septic shock includes antibiotics, maintenance of your blood pressure and support of your vital functions.

The study will recruit patients who are admitted to hospitals within approximately 50 centres in Europe and in the United States. It is expected that approximately 450 patients will be enrolled in this study.
What procedures are involved?

You have been proposed to take part in this trial because you have been diagnosed with septic shock. Based on the way nangibotide works, it is known that treating patients early in this situation provides the best opportunity for drugs to work; therefore, patients will be included in the trial within 24 hours of the diagnostic of the septic shock defined by introduction of vasopressor medication. Before the start of the trial, the medical and nursing staff at the hospital will collect information about you. Several examinations and procedures will be required in connection with the study. If you or the people responsible for decisions regarding your care agree to your participation in the study, and if you meet all the conditions required to be enrolled in the study, you will undergo the tests and examinations described below.

If you are part of the trial, you will receive the experimental study drug as a continuous intravenous infusion of nangibotide or a matching placebo (placebo means a dummy treatment that contains no active ingredients) in addition to your standard of care. You will be treated with study drug for at least 3 days. If you will still require vasopressors after the first 3 days, you will be treated until 24 hours after your shock has stopped, with a maximum treatment duration of 5 days. The medical and nursing staff will monitor your condition closely while you receive the trial medication. The care provided in the study will not replace your regular medical care. When your treatment with the drug under investigation is terminated, you will be followed up to day 7 to know how your body is reacting to the treatment.

You will be required to attend certain additional visits as mentioned below. Your participation in the study will last for a maximum of 1 year (including the follow-up visits).

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Time Window</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 10</td>
<td>±1d day</td>
</tr>
<tr>
<td>Day 28</td>
<td>+4 days</td>
</tr>
<tr>
<td>Day 90</td>
<td>±4 days (by phone)</td>
</tr>
<tr>
<td>6 months</td>
<td>±1 week (by phone)</td>
</tr>
<tr>
<td>12 months</td>
<td>±1 week (by phone)</td>
</tr>
</tbody>
</table>

Standard assessments for the monitoring of septic shock will be conducted during the study, including laboratory tests of blood samples, heart rate, temperature, breathing rate and blood pressure, physical examinations including height and weight (if these cannot be obtained, they may be estimated), electrocardiogram (ECG – recording of the electrical activity of your heart) and review of any changes in your health (adverse events, [AEs]). These assessments will help the physician monitor the course of your disease and evaluate how the drug is tolerated and whether it is beneficial for you. You will be asked about new hospitalizations, other infections (only D28) and your quality of life after 28 days, 90 days, 6 months and 12 months. Discharge letters from the intensive care unit, from the hospital and for every hospitalization starting before day 28 may be also collected.

This study will employ a randomized, 3-arm adaptive design. This means that patients will be put randomly (“by chance”, like flipping a coin) into groups. Each group will then receive a different treatment, and these groups will be compared at the end of the study.

You will have a 1 out of 3 chance to get into 1 of the 3 treatment arms (placebo, nangibotide 0.3 mg/kg/h or nangibotide 1.0 mg/kg/h).

Neither you nor your study doctor will know which treatment you are receiving. This is done to ensure that the results of the trial are not influenced and are fair; a double-blind trial helps make sure that the results are not affected by doctors’ or patients’ personal preferences. However, the medical staff can find out which trial medication you are receiving if they need to. The trial medication needs to remain unknown (blinded) until the trial data are analyzed. You may access this information only after the data have been analyzed.
In addition, the conduct of the study and the wellbeing of the patients are monitored on an ongoing basis by an experienced team of physicians and experts. These experts are independent from the sponsor and the treating physicians and can make recommendations on modification of the trial or even terminating the trial earlier if there is any safety concern related to nangibotide.

**Laboratory samples**

The laboratory tests of blood samples will be used to assess the following:

- The drug levels in your blood
- A potential reaction of your immune system against the study drug
- Several other markers in your blood, from which the researchers can examine the actions of nangibotide or the cause and treatment of septic shock in general

Biological samples may be collected, processed and reported as necessary for the purposes of the study. A part of the blood samples will be analyzed in the hospital’s laboratory where you are treated as part of your routine care. When the results are available, the samples will be destroyed according to the hospital’s regulations. Another part of the blood samples will be sent to external laboratories for analysis.

These samples will initially be stored at the hospital where you are treated until they are sent to the assigned laboratories. These samples will be coded and will not contain any personal identifying information. All samples will be kept in a secure place and will be destroyed after the analyses are complete. Samples will be stored in a repository for 5 years after the last follow-up visit at 12 months. The name and location of the repository can be requested throughout your study doctor. Ask your study doctor if you would like to have a detailed overview about the schedule of assessments during each visit.

The total blood volume sampled during the study until day 28 in addition to standard care for each patient will be approximately 170 mL but will not exceed 250 mL in any case. No blood samples will be collected after day 28.

**Future research**

Inotrem S.A. would like to save your leftover samples to use them in further research beyond this study to advance medical progress. Inotrem S. A. cannot currently specify the specific research objectives and projects of such research, but the projects will always be designed to learn about medical science and improve human health, such as aiming to understand, detect and predict diseases; develop new uses of or new medical products; or learn from past studies and past research. This can include your disease or other diseases. No genetic analyses on the leftover samples are planned.

**What is expected from you?**

All the patients included in a clinical study in France must be affiliated to a Social Security Scheme or be a beneficiary of one. When deciding whether to participate, consider whether you are able and willing to do the following:

- Tell the study doctor if you participated in another interventional study (study with investigational therapy or diagnostic procedure) in the 3 months prior to entering into this study.
- Fully cooperate in the smooth running of this trial and follow the study rules.
- Tell the study doctor truthfully about your complete medical history.
- Commit the time required to keep appointments.
- Report any new problems, illnesses or changes in medication during the study.
- Attend a follow-up visits at the study hospital after 28 (+4) days and additional follow-up visits via telephone call after 90 (±4) days, 6 months (±1 week) and 12 months (±1 week).
- Answer questions related to your health status, quality of life and hospital visits at the follow-up visits.

If you wish so, your general practitioner can be informed of your participation in this study.
What will happen at the end of the study?
Following the end of the study treatment or after you have withdrawn from the study before its conclusion, your study doctor (or appointed delegate) may seek to assess your long-term health status for a period of not more than 12 months, by contacting you to ascertain this information and to ask questions about your health status, quality of life and hospital stays. If you do not want this information about you to be collected, you may record your objection with your study doctor at any time.

What are the potential risks and discomforts?
In two previous studies (one in healthy volunteers and one in septic shock patients), nangibotide was found to be safe and well tolerated up to the highest dose tested.

However, side effects of nangibotide treatment may occur, and one of the reasons for this study is to learn more about the possible side effects of nangibotide. There may be risks that we cannot predict or rare or unknown side effects that could occur.

This study is conducted in hospitals that are experienced in the treatment of patients with septic shock and that ensure the close medical supervision of patients. The potential risks associated with the participation in this research trial will be explained to you (or your representative) before you make the decision to participate or not. The medical and nursing staff will follow your condition closely from the onset of septic shock and will monitor and treat any possible side effect.

If you experience any symptoms (even if you think they are not related to the trial) during the trial, you should inform your study doctor or nurse. You may not be well enough to tell the medical and nursing staff if you experience any of these symptoms, so the team of doctors and nurses will monitor you carefully to guarantee the best treatment for you during the trial period.

Few people have been exposed to nangibotide. So far, no side effects to nangibotide have been identified, so one of the purposes of this study is to learn more about the potential side effects of nangibotide. The most common and expected side effects and discomforts reported in the previous studies were due to the severe septic shock condition or the medical interventions used to treat the condition, which included vasopressor therapy, mechanical ventilation or renal replacement therapy.

No allergic reactions to nangibotide occurred in any prior trials. Sometimes, people may experience sensitivity/allergic reactions to medications. A sensitivity/allergic reaction may include itching; rash; hives; difficulty breathing; tightness in the chest; swelling of your face, lips, mouth, or tongue; and wheezing.

Nangibotide is a peptide (small protein), which means that your body can potentially recognize it as a foreign body and form antibodies to it. The possibility that you react against nangibotide is very low because this investigational drug is derived from a normal protein of your own body. However, this possibility still exists. We will collect blood samples throughout the study at selected timepoints to assess the development of nangibotide antibodies (immunogenicity tests). There was no development of such antibodies in the subjects who received nangibotide in the previous clinical studies.

When a sample of your blood is collected, you may experience some temporary discomfort, bruising, swelling and/or, in rare circumstances, infection at the needle site. Please tell the study doctor or study staff if you do not feel well after having your blood drawn. Nevertheless, most of the blood samples will be drawn from a catheter inserted in an artery as part of the standard of care in septic shock. In this case, no specific discomfort is expected.

The electrical activity of the heart (i.e., an ECG) will be traced daily until end of infusion of study drug. The ECG device has small wires that are attached to your body using adhesive patches in several places. You may experience temporary discomfort (pulling on the skin/skin hair) during the removal of the adhesive patches.
Inotrem S.A., MOT-C-203

After you have an ECG, you may have mild irritation, slight redness and itching at the places on your skin where the recording patches are placed.

Are there any reproductive risks?
It is not known if the study treatment may affect an unborn child or nursing infant. For this reason, if you are breast-feeding or pregnant, you may not participate in this study. Due to the nature of this study, even if you are in age of becoming pregnant, there is no need to use an acceptable method of birth control throughout the entire study.

Are there benefits to taking part in the study?
Taking part in this study may or may not make your condition better. It is possible that nangibotide may help improve your condition, but you may also not personally benefit from your participation in this study. However, by taking part, you will provide new information that may benefit other patients with septic shock in the future.

Are there any alternative treatments?
Currently, there is no treatment available that works on the cause of septic shock. Nangibotide targets the abnormal immune response seen during septic shock and will be administered in addition to the standard of care for your condition. Standard of care for septic shock includes antibiotics, maintenance of your blood pressure and organ support. If you choose not to take part, you will continue to receive the same standard and level of care as any patient with septic shock.

Will you be informed if new information becomes available during the study?
Your study doctor will inform you or your legal representative / trusted person / family member in a timely manner of any new information learned during the study that may affect your willingness to continue your participation.

Who can you contact with further questions?
If you require emergency care, tell the physician you consult about your participation in this study. In parallel contact also the study doctor or study staff as soon as possible. You can call the study doctor or study staff at any time if you have any concerns, questions or if you need to express complaints, at the phone number listed on page 1 of this form.

A description of this clinical trial will be available on public websites, including clinicaltrialsregister.eu and ClinicalTrials.gov. These websites will not include information that can identify you. You can search the websites at any time. The websites only show data in English, but you can request information from the study staff at any time and have access to data that are public.

What happens if you change your mind?
Your participation in this study is voluntary. You do not have to take part, and you may discontinue your involvement at any time without penalty or loss of benefits to which you are otherwise entitled. If you decide to leave the study before the last study visit, tell the study doctor and follow instructions. It may be helpful if you could explain the reason for your decision to leave the study, but you are not obliged to give any reason. If you condition still requires, you may receive standard treatment, and no prejudice will be shown towards you for medical care or participation in future research.

In addition, your study doctor or the sponsor may withdraw you from the study for your own safety, even if you wish to continue to participate, as in the following circumstances:
- If the study continuation would be detrimental to your well-being.
- If you will require a concomitant medication that represents a risk in combination with the study drug
- If you experience a study-related injury.
- If the trial is terminated by the sponsor.
If your participation in the study is stopped early, you may be asked to complete end-of-study procedures (such as a final medical examination and laboratory tests) for your own safety.

You also have the right to withdraw your consent for the further research of blood samples, as previously mentioned, at any time without providing any reason (including requesting the destruction of the sample). Please explicitly state to the study doctor that you want to withdraw your consent for further research. Any future use, processing and transfer of your blood samples will cease, and the samples will be destroyed as soon as possible. However, your decision to withdraw your consent for further research will not affect any processing, testing or research that has already been done on your personal information, coded data and samples. This is to guarantee that the study results are valid and comply with regulatory requirements. Withdrawal from further research will have no effect on your participation in the study.

Are there any costs if you decide to participate?
You will not receive payment for participating in this study, but the study drugs will be made available to you at no charge, and you will not be required to pay for any study procedures. You may be reimbursed for any reasonable travel expenses (bus/train/taxi fares) incurred as a result of taking part in this study on production of a receipt.

Reimbursement of your travel costs will be delegated to an independent company (FM Richard, 1 Place d ’Estienne d’Orves 75009 Paris) which will process your data according to the French law. The investigator or site personnel will address your travel receipts, received either from yourself or directly from the transportation companies, to FM Richard. In order to provide their services, FM Richard will have access to your name, surname and bank account. After the reimbursement, FM Richard will securely maintain your data in archive records for 10 years to comply with French legislation; after this period your data will be destroyed.

Are you insured when you participate in the study?
It is important that you tell your study doctor if you feel you have been injured because of taking part in this study. If needed the injury related to your study participation will be supported. You will get medical treatment if you are injured as a result of taking part in this study. Your study doctor will explain the treatment options to you and tell you where you can get adequate treatment.

INOTREM has taken out an insurance policy (contract No. 0100534514058 190059) with “HDI Global SE, Tour Opus 12, Defense 9, 77 Esplanade du General de Gaulle, 92914 Paris La Defense Cedex “, covering its civil liability as well as liability in respect of the various contributors to the research towards patients and their successors in law, in compliance with article L 1121-10 of the French Code of Public Health modified by the French law 2012-300 dated 05 Mar 2012 as modified by the order n°2016-800 dated 16 Jun 2016 and decree n°2016-1537 dated 16 Nov 2016

Sponsor assumes the indemnification where an injury is likely to have been caused by study treatment or study procedure in the case this injury would be attributable to the sponsor.
When sponsor’s responsibility is not engaged, victims can receive a compensation according to article L 1142-3 (Health Public code)

You can consult this attestation on investigational site on demand.

How will your confidentiality be respected and the privacy of your personal information maintained?
INOTREM is intended to utilize the data from this clinical - if successful - for the registration of nangibotide as treatment for septic shock or related conditions in Europe and other regions. Therefore, the results and records of this study including the clinical database may be transferred to third parties outside of France. This may include
foreign regulatory authorities and future partners of INOTREM. The data transferred will not contain information that will allow to reveal your identity.

- The department’s study site where the study takes place will record personal details about you, including your name, contact details, gender, height, weight and ethnic origin (to be used only for clinical purposes), as well as information on your medical history and clinical data collected about your participation in the study. The following people may also access these records:
  - Study monitors and auditors, who may work for Inotrem S.A. or its authorized agents, who will check that the study is being performed correctly and that the information collected about you is accurate;
  - Other employees or students of Inotrem S.A. or its authorized agents, who may accompany study monitors and auditors for quality and training purposes;
  - National and international regulatory authorities involved in keeping research safe for participants; and

To ensure privacy, your name and other directly identifying information will not be attached to records or samples released to Inotrem S.A. and its service providers for research purposes. Instead, you will only be identified by a code. Only the study doctor and authorized personnel will be able to connect this code to your name, by a list that will be kept securely by the study site for 15 years. Your coded data will be forwarded to Inotrem S.A. and its service providers for the analysis of the study. If the results of the study are published, your identity will remain confidential. A list of companies to which your coded information is transferred will be available from Inotrem S.A. via your study doctor.

If you wish, information relating to the overall results from the study can be given to you at the end of the research (article L.1122-1 of the Public Health Code).

Under European Union data protection law (the Data Protection Directive, replaced on 25 May 2018 by the General Data Protection Regulation), both the study doctor and Inotrem S.A. make important decisions on how your information are used and disclosed and shall be jointly responsible as ‘controllers’ for ensuring that the rules of this law are followed.

Your information is collected, used and disclosed in the study mainly based on the legitimate interests of Inotrem S.A. in conducting scientific research, or in certain circumstances based on legal obligation, for example to allow Inotrem S.A. to prove the results of the study or to report any side effects you may experience with the experimental drug. You are asked to consent to specific uses and disclosures of your information at the end of this form.

You have the right to access, through your study doctor, all the information collected about you and, if applicable, ask for corrections. You have the additional rights to object to how your information is being handled, request deletion of your data, restrict aspects of the processing of your information or ask for a copy of your data to be provided to you, or a third party, in a digital format. In certain circumstances these rights may be restricted to protect the study, for example, to protect the scientific integrity of the study, the treatment you receive in this study needs to remain unknown (i.e., blinded) until the study data are analyzed.

You also have the right to complain about how your information is handled to a supervisory authority that is responsible for enforcing data protection law in France the CNIL. A list of European Union supervisory authorities is available here: http://ec.europa.eu/justice/data-protection/article-29/structure/data-protection-authorities/index_en.htm

Recipients of your information may be in countries that do not provide the same standard of legal protection for your information as in the European Union, raising the risk that you will not be able to enforce the above rights and recipient organizations may not be legally required to fully secure your data. Certain international recipients of your information may have signed special contracts to provide legal protection for your transferred information.
Inotrem S.A., MOT-C-203

information (e.g., so-called “Standard Data Protection Clauses”). In any event, all parties involved in the study are required to maintain your confidentiality and the data transferred will not contain information that will allow to reveal your identity.

If you should withdraw from the study, data collected prior to your withdrawal may still be processed along with other data collected as part of the study. Normally, no new information will be collected for the study database unless you specifically consent to that. However, the law does require that any side-effects you may suffer are documented. You have the right to require that any previously retained samples are destroyed.

This study may only be performed by collecting and using personal information about study participants, as described in this form; therefore, you may only participate in the study if you agree to the collection and use of your information as described here.

If you have any questions, comments or complaints about how your information is handled in this study or wish to obtain a copy of the Standard Data Protection Clauses, you should first contact your study doctor, who will be able to direct your query, where appropriate, to the staff responsible for data protection at Inotrem S.A. (dpo@inotrem.com) or at the site where the study is conducted, including the site Data Protection Officer.

What will happen to your data?
By signing this form, you provide specific consent for the following:

- The authorized representatives of Inotrem S.A. and regulatory authorities’ inspectors may have direct access to your medical records.
- Study data, including your coded medical information, may be withdrawn and later used for further research into your medical indication, unless you object.
- Study data may be transferred to other countries for study purposes, including countries not providing the same standard of legal protection for your personal information as in the European Union.

Electronic health records (EHRs) will be used during the study.

Who has approved this research?
This study is being conducted in accordance with French 2012-300 dated 05 Mar 2012 as modified by the order n°2016-800 dated 16 Jun 2016 et decree n°2016-1537 dated 16 Nov 2016, and French and international Good Clinical Practices.
This study has been approved on (date) by the (EC number and name), organizations that are responsible for protecting the rights and safety of patients who take part in the study.
This study received Clinical Trial Authorization from the French Competent Authority (ANSM) on 19 September 2019.
INFORMED CONSENT FORM - SIGNATURE PAGE

In case the patient is capable to give informed consent

☐ Not Applicable

<table>
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<tr>
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- I have read and understood this information sheet.
- I have had the opportunity to ask questions, and I am satisfied with the explanations provided.
- I voluntarily agree to take part in this study.
- I am absolutely free to refuse to participate or terminate my participation.
- I know I can ask questions at any time by contacting the study doctor with the contact details specified on page 1 of this document.
- I understand that I will receive a copy of this signed and dated written consent form.
- By signing this form I specifically authorize my information to be checked, transferred and processed as follows: The authorized representatives of Inotrem S.A., and regulatory authorities’ inspectors may review my medical information by direct access to my medical records.
- Study data, including my coded medical information, and the results of analyses of any medical sample taken, may be used and shared for legitimate study and scientific purposes. This is applicable also, for future use in medical or pharmaceutical research if you do not object.
- The study data may be transferred to countries for processing, including countries that do not have the same legal protections for personal information, but all recipients will maintain confidentiality.
- I do not waive my rights or exempt the study doctor or sponsor from their legal and professional obligations
- I confirm that I am registered to a Social Security Scheme or am a beneficiary of one
Inotrem S.A., MOT-C-203

- I confirm that I am not subjected to any measure of legal protection (legal guardian, curatorship or judicial protection)

I agree to that my leftover samples are used for further research purpose.
- Yes
- No

I agree to that my general practitioner is informed about my participation in this clinical study.
- Yes
- No

Patient
Printed First/Last name  Signature  Date/Time (personally added)

I, the undersigned, investigator, confirm that I have verbally provided the necessary information about the study. I confirm that no pressure was applied to persuade the patient to agree to take part in the study and that I am willing to answer any additional questions if required. I state that the person signed above is not under legal guardianship, curatorship or judicial protection or incapable of giving consent personally as defined by Article L.1121-8 of the French public health code

Investigator
Printed First/Last name  Signature  Date /Time (personally added)

Those documents will be established in two originals. One of them will be given to the patient, the other one will be kept by the investigator.
### INFORMED CONSENT FORM - SIGNATURE PAGE

#### In case legal representative / trusted person / family members signs on behalf of the patient

- **Not Applicable**

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Patient should sign the continuation of trial participation page as soon as medical condition allows.

**For the attention of the legal representative / trusted person / family member:** Because of his/her clinical situation, the person you represent is not currently deemed capable of deciding whether or not to participate with full awareness of the implications. You are therefore being invited to decide whether he/she should participate in this clinical study, taking into consideration his/her likely wishes. (Article L1122-1-3 of Health Public Code)

**Legal representative / trusted person / family member** declare that I have been informed that I am being asked to take a decision on whether or not to take part in the clinical study for the person I represent in his/her best interests and taking into consideration his/her likely wishes. My consent applies to all the items listed in the consent of the participant. To my knowledge, the patient did not refuse his consent before the occurrence of his disability. I confirm that the patient has received information adapted to his ability to understand. I have also been informed that as soon as the clinical situation allows, the person I represent will be made aware of his/her participation in a clinical study and from that point will be free to continue with this participation or end it by signing or refusing to sign this consent form. I will receive a signed and dated copy of the information to the participant and the informed consent form.

I agree to that leftover samples of patients are used for further research purpose.

MOT-C-203 France English ICF Main 2.0_19Sep2019
I agree to that general practitioner of patient is informed about his/her participation in this clinical study.

☐ Yes
☐ No

Legal representative / trusted person / family member*

Printed First/Lastname | Signature | Date/Time (personally added) and relationship to the person represented:

* If Mr/Mrs/Miss………… is currently not autonomous for reading and/or writing, the third party (trusted person) identified below confirms that he or she has personally and carefully read the information document and the present informed consent form to the subject and obtained the latter's approval to sign the document here on his or her behalf.

I, the undersigned, investigator, confirm that I have verbally provided the necessary information about the study. I confirm that no pressure was applied to persuade the patient’s representative to agree to take part in the study and that I am willing to answer any additional questions if required.

I state that the person signed above is not under legal guardianship, curatorship or judicial protection or incapable of giving consent personally as defined by Article L.1121-8 of the French public health code

The patient / representative will receive a copy of the signed and dated Informed Consent Document (including both the Informed Consent Form - Signature Page and the related Patient Information).

Investigator

Printed First/Lastname | Signature | Date /Time of signature
## AUTHORIZATION’s FORM - SIGNATURE PAGE

**In case independent physician signs on behalf of the patient**

- Not Applicable

### NAME OF STUDY:

Efficacy, Safety and Tolerability of Nangibotide in Patients with Septic Shock.  
A Randomized, Double-blind, Placebo Controlled Dose Selection Study  
The ASTONISH Study

### STUDY NUMBER:

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131824

### STUDY SPONSOR:

Inotrem S.A.  
114 Rue La Boétie  
75008 Paris  
France

### STUDY DOCTOR (INVESTIGATOR):

[Investigator Name]  
[Site Address]  
[Office Hours Tel]  
[Out of Hours Tel]

### PATIENT ID NUMBER


### PATIENT FIRSTNAME / LASTNAME


Patient should sign the continuation of trial participation page as soon as medical condition allows:

**Independent Physician**

If informed consent cannot be obtained from a patient or his/her representative due to urgency and if the conditions set out in Article L.1122-1-3 concerning experiments on humans are met, an independent physician, will determine if the patient could potentially benefit from study participation. An independent physician is a physician who is not the patient’s treating physician, is independent of the trial and cannot be influenced by people involved with the trial. The patient or the patient’s legal authorized representative will be informed about the trial as soon as possible and consent to continue will be requested. If the patient or the patient’s legal authorized representative does not agree to give consent, the patient will be withdrawn from the study.

---

**Independent Physician**  
Printed First/Lastname  
Signature  
Date/Time (personally added)
I, the undersigned, investigator, confirm that I have verbally provided the necessary information about the study. I confirm that no pressure was applied to persuade the independent physician to agree for patient to take part in the study and that I am willing to answer any additional questions if required.

The patient / representative will receive a copy of the signed and dated Informed Consent Document (including both the Informed Consent Form - Signature Page and the related Patient Information).

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Consent for continued trial participation - In case the patient is capable to give informed consent

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PATIENT ID NUMBER

PATIENT FIRSTNAME / LASTNAME

For the attention of the patient: When you were included in the study, you were incapable to decide for yourself whether or not to take part in this study. It was then either customary to use a patient’s representative or an independent physician, who was asked to make a decision on your participation in the study in your best interests and taking into consideration your likely wishes.

Your legal authorized representative / independent physician agreed to your participation in this study, knowing that once your clinical situation allowed, you will be informed of your participation in a clinical study and from that point will be free to continue with this participation or end it.

Patient:
I am currently participating in a clinical research trial in which consent for my participation was initially obtained from my representative or an independent physician as a result of my inability to provide consent at the time. I have now recovered to the point where the study doctor believes that I am able to consent to continued participation in this clinical research trial.

- I have read and understood this information sheet.
- I have had the opportunity to ask questions, and I am satisfied with the explanations provided.
- I voluntarily agree to continue my participation in this clinical research trial.
- I am absolutely free to refuse to continue or terminate my participation.
Inotrem S.A., MOT-C-203

- I know I can ask questions at any time by contacting the study doctor with the contact details specified on page 1 of this document.
- I understand that I will receive a copy of this signed and dated written consent form.
- By signing this form I specifically authorize my information to be checked, transferred and processed as follows: The authorized representatives of Inotrem S.A., and regulatory authorities’ inspectors may review my medical information by direct access to my medical records.
- Study data, including my coded medical information, and the results of analyses of any medical sample taken, may be used and shared for legitimate study and scientific purposes. This is applicable also, for future use in medical or pharmaceutical research if you do not object.
- The study data may be transferred to countries for processing, including countries that do not have the same legal protections for personal information, but all recipients will maintain confidentiality.
- I do not waive my rights or exempt the study doctor or sponsor from their legal and professional obligations.
- I confirm that I am registered to a Social Security Scheme or am a beneficiary of one.
- I confirm that I am not subjected to any measure of legal protection (legal guardian, curatorship or judicial protection).

I agree to the use of data previously collected when I was unable to consent

☐ Yes
☐ No

I agree that my leftover samples are used for further research purpose.

☐ Yes
☐ No

I agree to that my general practitioner is informed about my participation in this clinical study.

☐ Yes
☐ No

Patient
Printed First/Lastname  Signature  Date/Time (personally added, the undersigned, investigator, confirm that I have verbally provided the necessary information about the study. I confirm that no pressure was applied to persuade the patient to agree to continue in the study and that I am willing to answer any additional questions if required. I state that the person signed above is not under legal guardianship, curatorship or judicial protection or incapable of giving consent personally as defined by Articles L. 1121-8 of the French public health code.

The patient will receive a copy of the signed and dated Informed Consent Document (including both the Informed Consent Form - Signature Page and the related Patient Information).

Investigator
Printed First/Lastname  Signature  Date /Time
INFORMED CONSENT FORM - SIGNATURE PAGE

Consent for continued trial participation - In case legal representative / trusted person / family member signs on behalf of the patient

☐ Not Applicable

<table>
<thead>
<tr>
<th>NAME OF STUDY:</th>
<th>Efficacy, Safety and Tolerability of Nangibotide in Patients with Septic Shock. A Randomized, Double-blind, Placebo Controlled Dose Selection Study The ASTONISH Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>STUDY NUMBER:</td>
<td>MOT-C-203</td>
</tr>
<tr>
<td>EudraCT NUMBER:</td>
<td>2018-004827-36 131824</td>
</tr>
<tr>
<td>STUDY SPONSOR:</td>
<td>Inotrem S.A. 114 Rue La Boétie 75008 Paris France</td>
</tr>
<tr>
<td>STUDY DOCTOR (INVESTIGATOR):</td>
<td>[Investigator Name] [Site Address] [Office Hours Tel] [Out of Hours Tel]</td>
</tr>
<tr>
<td>PATIENT ID NUMBER</td>
<td></td>
</tr>
<tr>
<td>PATIENT FIRSTNAME / LASTNAME</td>
<td></td>
</tr>
</tbody>
</table>

For the attention of the legal representative / trusted person / family member: Because of his/her clinical situation, the person you represent is not currently deemed capable of deciding whether or not to continue participation with full awareness of the implications. You are therefore being invited to decide whether he/she should participate in this clinical study, taking into consideration his/her likely wishes. (Article L1122-1-3 of Health Public Code)

Legal representative / trusted person / family member declare that I have been informed that I am being asked to take a decision on whether or not to continue the participation in the clinical study for the person I represent in his/her best interests and taking into consideration his/her likely wishes. My consent applies to all the items listed in the consent of the participant. To my knowledge, the patient did not refuse his consent before the occurrence of his disability. I confirm that the patient has received information adapted to his ability to understand. I have also been informed that as soon as the clinical situation allows, the person I represent will be made aware of his/her participation in a clinical study and from that point will be free to continue with this participation or end it by signing or refusing to sign this consent form. I will receive a signed and dated copy of the information to the participant and the informed consent form.
I agree to the use of data previously collected for the person I represent

- Yes
- No

I agree to that his/her leftover samples are used for further research purpose.

- Yes
- No

I agree to that his/her general practitioner is informed about his/her participation in this clinical study.

- Yes
- No

Legal representative / trusted person / family member*

<table>
<thead>
<tr>
<th>Printed First/Lastname</th>
<th>Signature</th>
<th>Date/Time (personally added)</th>
</tr>
</thead>
<tbody>
<tr>
<td>and relationship to the person represented:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* If Mr/Mrs/Miss………… is currently not autonomous for reading and/or writing, the third party (trusted person) identified below confirms that he or she has personally and carefully read the information document and the present informed consent form to the subject and obtained the latter’s approval to sign the document here on his or her behalf.

I, the undersigned, investigator, confirm that I have verbally provided the necessary information about the study.

I confirm that no pressure was applied to persuade the patient’s representative to agree to take part in the study and that I am willing to answer any additional questions if required.

I state that the person signed above is not under legal guardianship, curatorship or judicial protection or incapable of giving consent personally as defined by Article L.1121-8 of the French public health code.

* The patient / representative will receive a copy of the signed and dated Informed Consent Document (including both the Informed Consent Form - Signature Page and the related Patient Information).

Investigator

<table>
<thead>
<tr>
<th>Printed First/Lastname</th>
<th>Signature</th>
<th>Date /Time</th>
</tr>
</thead>
</table>

MOT-C-203 France English ICF Main 2.0_19Sep2019

Page 19 of 20

**SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents**

<table>
<thead>
<tr>
<th>Section/item</th>
<th>Item No</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Administrative information</strong></td>
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<tr>
<td>Title</td>
<td>1</td>
<td>Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Completed Line 1</td>
</tr>
<tr>
<td>Trial registration</td>
<td>2a</td>
<td>Trial identifier and registry name. If not yet registered, name of intended registry</td>
</tr>
<tr>
<td></td>
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<td>Completed Line 48</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>All items from the World Health Organization Trial Registration Data Set</td>
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<tr>
<td></td>
<td></td>
<td>Completed throughout document</td>
</tr>
<tr>
<td>Protocol version</td>
<td>3</td>
<td>Date and version identifier</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Protocol version 3.0 (3.1 in France) 04th February 2020</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Protocol version 4.0(4.1 in France) with specific instructions for handling COVID-19 patients – 25th March 2020</td>
</tr>
<tr>
<td>Funding</td>
<td>4</td>
<td>Sources and types of financial, material, and other support</td>
</tr>
<tr>
<td></td>
<td></td>
<td>This study is supported by Inotrem SA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Line 448</td>
</tr>
<tr>
<td>Roles and responsibilities</td>
<td>5a</td>
<td>Names, affiliations, and roles of protocol contributors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>See text</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Line 9</td>
</tr>
<tr>
<td></td>
<td>5b</td>
<td>Name and contact information for the trial sponsor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dr Jean Jacques Garaud</td>
</tr>
<tr>
<td></td>
<td></td>
<td>INOTREM S.A.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>54 Rue de Ponthieu</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75008 Paris</td>
</tr>
<tr>
<td></td>
<td></td>
<td>France</td>
</tr>
</tbody>
</table>
Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities.

The sponsor or its designated representatives are responsible for study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication. The sponsor is committed to open access publishing of the trial report.

Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee).

Coordinating centre: St Luc Clinical coordinating centre (Belgium), Ocean State CCC (Providence, Rhode Island, USA)
Data adjudication committee: (Judgments on a per patient basis on: Appropriate antibiotics, septic shock steroids, septic shock related mortality)
Data Management team: CRO: PPD ltd
Safety and pharmacovigilence: Stragen Services plc

**Introduction**

**Background and rationale**

Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention.

See text Line 101

**6b** Explanation for choice of comparators

See text
Line 154

**Objectives**

Specific objectives or hypotheses

See text
Line 118

**Trial design**

Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

See text
Line 219
Methods: Participants, interventions, and outcomes

Study setting  9  Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

See text
Line 139

Eligibility criteria  10  Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

See text
Table 1

Interventions  11a  Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

See text
Line 152

11b  Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)

See text
Line 296

11c  Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

See text
Line 205

11d  Relevant concomitant care and interventions that are permitted or prohibited during the trial

See text
Line 152

Outcomes  12  Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

See text
Line 168
Participant timeline

13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)

See text
See Figure 1

Sample size

14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations

See text
Lines 224 to 233

Recruitment

15 Strategies for achieving adequate participant enrolment to reach target sample size

See text
Line 141

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

See text
Line 221

Allocation concealment mechanism 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

See text
Line 216

Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions

See text
Line 222

Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
See text
Line 163

17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial
See text
Line 165

**Methods: Data collection, management, and analysis**

**Data collection methods**

18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
See text
Line 174
Line 333
Supplementary file

18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
See text
Line 296

**Data management**

19 Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
See text
Line 282

**Statistical methods**

20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
See text
Line 238

20b Methods for any additional analyses (e.g., subgroup and adjusted analyses)
See text
Line 270
Statistical Analysis Plan available on request
20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

See text
Line 251

**Methods: Monitoring**

Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

DMC charter attached as an appendix

21b Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

See text
Line 275

**Harms** 22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

See text
Line 209

**Auditing** 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Independent audit of selected study centres will be undertaken on at least five occasions during the study period to ensure compliance with study protocol and data quality.

**Ethics and dissemination**

Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

See text
Line 290

Protocol amendments 25 Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Clinical trials databases will be updated with protocol amendments 
Study sites will be updated in the event of protocol amendments 
IRBs/Regulatory bodies will approve all substantial amendments prior to implementation

<table>
<thead>
<tr>
<th>Consent or assent</th>
<th>26a</th>
<th>Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>See text Line 147</td>
</tr>
<tr>
<td>26b</td>
<td></td>
<td>Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>See text Line 296</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Confidentiality</th>
<th>27</th>
<th>How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>See text Line 301</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Declaration of interests</th>
<th>28</th>
<th>Financial and other competing interests for principal investigators for the overall trial and each study site</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>See text Line 453</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Access to data</th>
<th>29</th>
<th>Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Consistent with regulatory requirements, the trial data set will be published online without restriction.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ancillary and post-trial care</th>
<th>30</th>
<th>Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All appropriate insurance is in place to manage any trial associated harms.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dissemination policy</th>
<th>31a</th>
<th>Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>See text Line 300</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>31b</th>
<th>Authorship eligibility guidelines and any intended use of professional writers</th>
</tr>
</thead>
</table>
See author contribution text. No use of professional writers is projected at this time.

31c Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Open access publication of the protocol is proposed. The participant level data set and statistical code will not be available.

Appendices

Informed consent materials 32 Model consent form and other related documentation given to participants and authorised surrogates

See Appendix for exemplar consent form

Biological specimens 33 Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

See appendix

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.