



## CLINICAL STUDY PROTOCOL

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

#### **The ASTONISH Study**

|                                   |                                                             |
|-----------------------------------|-------------------------------------------------------------|
| <b>Test Product:</b>              | Nangibotide                                                 |
| <b>Sponsor:</b>                   | INOTREM S.A.<br>54 rue de Ponthieu<br>75008 Paris<br>France |
| <b>Sponsor's Medical Officer:</b> | Jean-Jacques Garaud, MD                                     |
| <b>Sponsor Protocol Number:</b>   | MOT-C-203                                                   |
| <b>EudraCT Number:</b>            | 2018-004827-36                                              |
| <b>IND:</b>                       | 131824                                                      |
| <b>Development Phase:</b>         | IIb                                                         |
| <b>Coordinating Investigator:</b> | Bruno François, MD                                          |
| <b>Version:</b>                   | 5.0                                                         |
| <b>Date:</b>                      | 17 January 2022                                             |

#### 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 authorization from INOTREM SA or its affiliates.

1 STUDY SYNOPSIS

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |                                                 |  |
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| Protocol No.: MOT-C-203                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  | Study Drug: Nangibotide                         |  |
| <b>Coordinating Investigator:</b><br>Bruno François, MD; Réanimation Polyvalente & Inserm CIC 1435 CHU Dupuytren;<br>87042 Limoges Cedex, France                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |                                                 |  |
| <b>Study Title:</b><br>Efficacy, Safety and Tolerability of Nangibotide in Patients with Septic Shock.<br>A Randomized, Double-blind, Placebo Controlled Dose Selection Study                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |                                                 |  |
| <b>Study Sites:</b><br>Multi-national, multi-center study with approximately 50 centers in Europe and the United States                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |                                                 |  |
| <b>Study Period (planned):</b> <ul style="list-style-type: none"><li>First patient first visit: October 2019</li><li>Last patient last visit (blinded): Q2/2022</li><li>Last patient last follow-up visit: Q2/2023</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  | <b>Development Phase:</b><br>Clinical Phase IIb |  |
| <b>Objectives:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |  |                                                 |  |
| <b>Primary</b> <ul style="list-style-type: none"><li>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 soluble TREM-1 (sTREM-1) plasma levels (patients with high sTREM-1 levels at baseline and all patients)</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |                                                 |  |
| <b>Secondary</b> <p>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:</p> <ul style="list-style-type: none"><li>To evaluate the effect of nangibotide on mortality for up to 12 months</li><li>To evaluate the effect of nangibotide on other clinical parameters (e.g. duration of shock, vasopressor use, ventilator and renal replacement use, secondary infections)</li><li>To evaluate the safety and tolerability of nangibotide</li><li>To evaluate the effect of nangibotide on quality of life, resource utilization and post shock morbidity</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |                                                 |  |
| <b>Exploratory</b> <ul style="list-style-type: none"><li>To evaluate PK/PD relationship to nangibotide-mechanism-of-action-related markers</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |  |                                                 |  |
| <b>Methodology</b> <p>This is a randomized, double-blind, placebo-controlled dose-selection study in which two doses of nangibotide are tested versus placebo.</p> <p>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 potential study patients will receive standard of care for the treatment of septic shock.</p> <p>After screening for eligibility, patients meeting all inclusion and no exclusion criterion will be randomized. The randomization will be stratified according to site.</p> <p>Patients will be randomized to one of three treatment arms. Patients will then either receive a 6.66 mg/kg/h loading dose (LD) of nangibotide for 15 minutes followed by a continuous intravenous (i.v.) infusion of nangibotide 0.3 mg/kg/h or a 20 mg/kg/h LD of nangibotide for 15 minutes followed by a continuous i.v. infusion of nangibotide 1.0 mg/kg/h or a matching placebo.</p> <p>The treatment with study drug will be on top of standard of care.</p> <p>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 (PK) and exploratory pharmacodynamic (PD) analyses will be collected before and throughout the treatment period.</p> <p>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).</p> <p>Patients will be assessed at the End of Study (EoS) visit at day 28. After the last patient’s day 28 visit, the study will be analyzed.</p> <p>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. Investigators, patients and study teams will be</p> |  |                                                 |  |

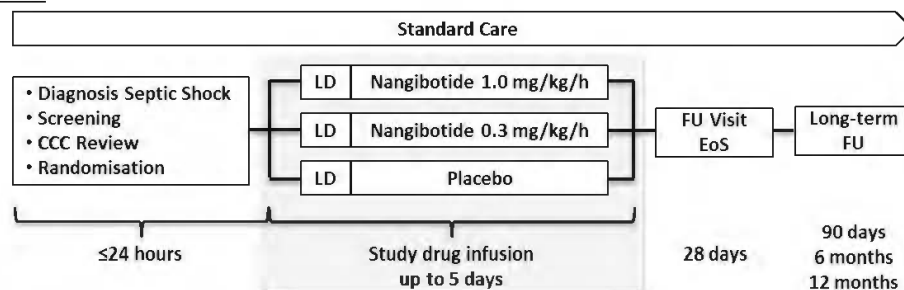
kept blinded to the fullest possible extent. Data of the long-term follow-up will be analyzed and reported separately.

An independent Data Monitoring Committee (DMC) will monitor the safety of the study on an ongoing basis. After the first 112 (25%) and 225 (50%) patients have completed the 7-day period after randomization, an unblinded interim analyses of safety will be performed and the data reviewed by the DMC. The second interim analysis will, in addition, include an analysis of efficacy data, after which the DMC will make recommendations for a potential adjustment of sample size or for stopping the clinical trial or a treatment arm for futility. Patient recruitment will not be stopped during the interim analyses.

An independent data adjudication committee (DAC) will review blinded study data before database lock. The responsibility of the DAC includes the assessment of the cause of death and the appropriateness of antibiotic therapy and source control.

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

#### Study Flowchart



LD: Loading dose or matching placebo; FU: Follow-up; EoS: End of Study

#### Number of Patients

A total of approximately 450 patients is planned in order to achieve 150 patients treated per arm.

**COVID-19:** due to the COVID-19 pandemic, which has impacted the pace of enrollment, the trial will be stopped earlier with at least 354 evaluable patients.

#### Diagnosis and Main Criteria for Inclusion

**Diagnosis:** Septic Shock (according to Sepsis-3 definitions)

##### Inclusion Criteria:

To be eligible for the study, patients must meet the following criteria:

1. Provide written informed consent (proxy/legal representative) according to local regulations
2. Age 18 to 85 years (inclusive)

##### Sepsis

3. Documented or suspected infection: lung, abdominal or urinary tract infection (UTI) in the elderly ( $\geq 65$  years)
4. Organ dysfunction defined as acute change in total SOFA score  $\geq 2$  points

##### Shock

5. Refractory hypotension requiring vasopressors to maintain MAP  $\geq 65$  mm Hg despite adequate volume resuscitation (as per recommendations of the Surviving Sepsis Campaign)
6. Hyperlactatemia (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

The presence of any of the following criteria will exclude a patient from study enrollment:

1. Previous episode of septic shock requiring vasopressor administration within current hospital stay
2. Underlying concurrent immunodepression with anti-CD52 alemtuzumab (Campath) or glucocorticoids  $> 75$  mg prednisone daily or equivalent for more than 7 days
3. Immunosuppressive therapy related to recent ( $< 6$  months) transplantation
4. Cancer chemotherapy ( $< 3$  months) implying an immunodepression
5. Known HIV infection with low CD4 cell count ( $< 200$ ) for at least 6 months
6. Known pregnancy (positive urine or serum pregnancy test)
7. Shock of any other cause, e.g. hypotension related to gastrointestinal bleeding
8. Ongoing documented or suspected endocarditis, history of prosthetic heart valves
9. Prolonged QT syndrome
10. End-stage neurological disease

- 
11. End-stage cirrhosis (Child Pugh Class C)
  12. Acute Physiology and Chronic Health Evaluation (APACHE II) score  $<15$  or  $\geq 34$
  13. Home oxygen therapy on a regular basis for  $> 6$  h/day
  14. Recent cardiopulmonary resuscitation (CPR) (within current hospital stay)
  15. Body mass index (BMI)  $\geq 40$  kg/m<sup>2</sup> or weight  $\geq 130$  kg
  16. Moribund patients
  17. Decision to limit full care taken before obtaining informed consent
  18. Participation in another interventional study in the 3 months prior to randomization
- 

**Test Product, Dose and Mode of Administration**

Nangibotide will be administered as continuous i.v. infusion for up to 5 days. At the start of treatment, there will be a LD of 6.66 or 20 mg/kg/h administered for 15 minutes followed by a maintenance dose of 0.3 or 1.0 mg/kg/h.

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**Reference Product, Dose and Mode of Administration**

Matching placebo

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**Duration of Treatment**

Study drug will be administered for at least 3 days ( $72 \pm 2$  hours) or until 24 ( $\pm 2$ ) hours after vasopressor cessation or for a maximum of five (5) days ( $120$  hours  $\pm 2$ ).

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**Duration of Clinical Study**

Duration of i.v. infusion: up to 5 days

Duration of follow-up: 28 days blinded, 1-year additional follow-up

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**Criteria for Evaluation****Primary Endpoint**

- Change of total SOFA score (improvement of organ dysfunction) from baseline to day 5 (in the subgroup defined by patients with elevated sTREM-1 baseline levels and in the overall population)

**Key Secondary Endpoint**

- Survival and all-cause mortality on D28

**Secondary Endpoints**Efficacy Parameters

- Duration of ICU stay, hospitalization
- Organ support free survival
- Sepsis support index (SSI)
- Daily change of total SOFA score and individual subscores
- Vasopressor use
- Invasive mechanical ventilation
- Renal support
- All-cause mortality up to 12 months
- Septic shock related mortality up to 12 months
- Incidence of secondary infections and post shock antibiotic use

Safety Parameters

- Vital signs: systolic (SBP) and diastolic (DBP) blood pressure, heart rate, and body temperature
- Electrocardiogram (12-lead ECG)
- Safety laboratory tests: hematology, coagulation, plasma biochemistry
- Presence of anti-nangibotide antibodies
- Adverse events (AEs), serious adverse events (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)
  - Post shock morbidity
  - Health care resource utilization
-

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## STATISTICAL METHODS

### Randomization and Stratification

Eligible patients will be randomized in a 1:1:1 ratio into 1 of the 3 treatment arms. Randomization will be stratified according to site.

### Efficacy Analyses

The primary efficacy endpoint is the change of SOFA from baseline to day 5, which will be analyzed on the modified ITT Set.

The primary efficacy endpoint will be tested in the subgroup defined by patients with elevated sTREM-1 baseline levels (i.e.  $\geq 400$  pg/mL) and in the overall population.

The analysis of the change of SOFA score from baseline to day 5 will be based on an ANCOVA model adjusting for randomized treatment (placebo and nangibotide doses) and the baseline SOFA score. The LS Mean change of SOFA for each treatment (placebo or nangibotide doses) and the difference in LS Means between placebo and the nangibotide doses will be estimated in this model along with their 95% confidence intervals.

### Key Secondary Endpoint

The All-cause mortality at day 28 will be analyzed in a logistic regression model adjusting for the same covariates used for the primary endpoint analysis. The treatment effect comparing each dose vs placebo will be estimated in terms of an odds ratio associated with the 95% CI and p-value.

### Secondary Endpoints Analyses

Usual statistics will be used for the analysis of the other secondary endpoints.

### Sample Size Determination

A total of approximately 450 patients is planned in order to achieve 150 patients treated per arm in the study.

The sample size determination is based on the primary endpoint, i.e. the change of SOFA score from baseline to day 5, tested in the subgroup of patients with elevated sTREM-1 levels (i.e.  $\geq 400$  pg/mL) and in the overall population. The power achieved with this scenario is at least 90% for the claim of at least one dose in the subgroup of patients with elevated sTREM-1 levels and for the claim of at least one dose in the overall population.

### Interim Analysis

An interim analysis will be performed on unblinded data and reviewed by DMC when about 225 patients have completed the 7-day period after randomization. This interim analysis aims to:

- perform a futility analysis for the study or for dropping a futile dose.
- Possibly increase the sample size to maintain the power of the pairwise comparisons of nangibotide vs placebo in the subgroup of patients with elevated sTREM-1 baseline levels (i.e.  $\geq 400$  pg/mL) if the proportion of patients with elevated sTREM-1 baseline levels (i.e.  $\geq 400$  pg/mL) in the interim sample is lower than 50%.

COVID-19: due to the COVID-19 pandemic, which has impacted the pace of enrollment, the trial will be stopped earlier with at least 354 evaluable patients, i.e. patients having completed the Day-28 assessment and with an available baseline sTREM-1 assessment. Despite a sample size lower than 450 and given the estimated interim proportion of patients with high baseline sTREM-1 levels that was higher than expected (~70% compared to 50%), the power of the analysis in the subgroup of patients with high baseline sTREM-1 levels and the power of the analysis in the overall population are still above 90%, while considering the same assumptions made for the determination of the initial sample size of 450 patients.

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## HISTORY OF CHANGES

Changes from version 4.0 dated 25 March 2020 to version 5.0 date 14 January 2022:

- PK sampling becomes optional as sufficient samples have been collected to support pharmacokinetic studies and in order to ease recruitment since the pharmacokinetic sampling procedure is technically difficult and not always easy to conduct at sites.
- Modification of the sample size according to the proportion of patients in the high sTREM-1 group

Changes from version 3.0 of the study protocol, dated 04 February 2020 to version 4.0, dated 25 March 2020 (non-substantial according to adaptive features of the study protocol)

- Accommodation of possibly limited blood sampling in patients with a concomitant diagnosis of Covid-19 ([section 12.19.6](#))
- Assessment of EQ5D for visit a day 28 updated

Changes from version 2.0 of the study protocol, dated 11 September 2019 to version 3.0, dated 04 February 2020

- Assessment of primary endpoint changed from day3 to day 5: "Change of total SOFA score (improvement of organ dysfunction) from baseline to *day 5* (in the subgroup defined by patients with elevated sTREM-1 baseline levels and in the overall population)"
- The handling of missing data was updated
- Assessment of body temperature updated
- Treatment regimen clarified ([section 10.3](#))
- Assessment of vital signs, ECG and SOFA score at screening clarified ([section 11.3.1](#))
- Reporting of overdosing added
- Minor corrections and clarifications
- Addresses of INOTREM and Stragen Services updated

Changes from version 1.0 of the study protocol, dated 26 April 2019 to version 2.0, dated 11 September 2019.

- Addition of an additional interim analysis and DMC review of safety data after 112 (25%) of patients randomized ([section 8.5](#))
- Addition of exclusion criteria " history of prosthetic heart valves" and "Prolonged QT syndrome"
- Addition of daily ECG measurements until end of study drug infusion
- Clarification of section "12.14 Study Drug Infusion and End of Vasopressor Definition", cross-reference with [section 10.3](#) added
- Reference to summary of product characteristics added for concomitant medications in [sections 10.7](#) and [11.5](#)
- Clarification of section "9.5 Withdrawal of Patients" and addition of the need for a concomitant medication representing a risk to the patient as criterion for withdrawal
- Clarification of adaptive features ([section 8.3](#)) regarding DMC and DAC
- Addition of paragraphs relating to data safety, accessibility and portability and feedback on incidental findings have been added to [section 17](#)
- Assessment of disseminated intravascular coagulation (DIC) removed

- Assessment of secondary infections stopped at day 28
- Change of address for ABF Pharmaceutical Services GmbH
- Minor corrections and clarifications

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**3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS**

|                 |                                                                       |
|-----------------|-----------------------------------------------------------------------|
| °C              | Degree Celsius                                                        |
| ADA             | Anti-Drug Antibody                                                    |
| AE              | Adverse event                                                         |
| AIDS            | Acquired Immune Deficiency Syndrome                                   |
| ANCOVA          | Analysis of covariance                                                |
| Ang             | Angiopoietin                                                          |
| APACHE          | Acute Physiology And Chronic Health Evaluation                        |
| BMI             | Body mass index                                                       |
| CA              | Competent Authorities                                                 |
| CCC             | Clinical coordination center                                          |
| CCI             | Charlson Comorbidity Index                                            |
| CI <sub>s</sub> | Confidence Intervals                                                  |
| CIV             | Continuous Intravenous Infusion                                       |
| CPR             | Cardiopulmonary resuscitation                                         |
| CRF             | Case report form                                                      |
| CRO             | Contract research organization                                        |
| d/D             | Day                                                                   |
| DBP             | Diastolic blood pressure                                              |
| DI              | Deciliter                                                             |
| DAC             | Data Adjudication Committee                                           |
| DHM             | Data Handling Manual                                                  |
| dL              | Deciliter                                                             |
| DMC             | Data Monitoring Committee                                             |
| DSUR            | Development Safety Update Reports                                     |
| EC              | Ethics committee                                                      |
| ECG             | Electrocardiogram                                                     |
| eCRF            | Electronic case report form                                           |
| EoI             | End of Infusion                                                       |
| EoS             | End of Study                                                          |
| EQ-5D           | EuroQol (5 dimensions)                                                |
| FU              | Follow-up                                                             |
| GCP             | Good clinical practice                                                |
| GLP             | Good Laboratory Practice                                              |
| GMP             | Good Manufacturing Practice                                           |
| h/H             | hour                                                                  |
| HIV             | Human immunodeficiency virus                                          |
| i.v.            | intravenous                                                           |
| ICF             | Informed consent form                                                 |
| ICH             | International council for Harmonization                               |
| ICU             | Intensive care unit                                                   |
| IMP             | Investigational medicinal product                                     |
| IMV             | Investigational Monitoring Visit (or) Invasive Mechanical Ventilation |
| INN             | International non-proprietary name                                    |
| IRB             | Institutional Review Board                                            |
| IRT             | Interactive Response Technology                                       |
| ITT             | Intent-to-treat                                                       |
| IUO             | Investigational Use Only                                              |
| Kg              | Kilogram                                                              |

|         |                                                          |
|---------|----------------------------------------------------------|
| KM      | Kaplan-Meier                                             |
| L       | Liter                                                    |
| LD      | Loading Dose                                             |
| LOCF    | Last Observation Carry Forward                           |
| LPLV    | Last patient last visit                                  |
| LR12    | Active pharmaceutical ingredient in MOTREM               |
| LS      | Least Square                                             |
| MAP     | Mean arterial pressure                                   |
| MAR     | Missing at                                               |
| MEDRA   | Medical dictionary for regulatory affairs                |
| mg      | Milligram                                                |
| µg      | Microgram                                                |
| Min     | Minute                                                   |
| mITT    | Modified intent-to-treat                                 |
| mL      | Milliliter                                               |
| mmol    | Millimole                                                |
| MNAR    | Missing not at random                                    |
| MOTREM  | Clinical formulation of LR12                             |
| MS      | Mass spectrometry                                        |
| NA      | Noradrenaline                                            |
| NE      | Norepinephrine                                           |
| NOAEL   | No Observed Adverse Effect Level                         |
| PD      | Pharmacodynamics                                         |
| PK      | Pharmacokinetics                                         |
| PP      | Per Protocol                                             |
| Q       | Quarter (calendar)                                       |
| q.s.    | Quantum satis                                            |
| QTc     | Corrected QT interval                                    |
| RRT     | Renal Replacement Therapy                                |
| RUO     | Research Use Only                                        |
| SAE     | Serious Adverse Event                                    |
| SAP     | Statistical Analysis Plan                                |
| SBP     | Systolic blood pressure                                  |
| SCR     | Screening                                                |
| SDV     | Source Data Verification                                 |
| SE      | Standard error                                           |
| SOFA    | Sequential Organ Failure Assessment                      |
| SPC     | Summary of Product Characteristics                       |
| SSI     | Sepsis Support Index                                     |
| sTREM-1 | Soluble Triggering Receptor Expressed on Myeloid Cells 1 |
| SUSAR   | Suspected unexpected drug reaction                       |
| TLT-1   | TREM Like Transcript 1                                   |
| TREM-1  | Triggering Receptor Expressed on Myeloid Cells 1         |
| UTI     | Urinary tract infection                                  |
| vs      | Versus                                                   |
| WHO     | World Health Organization                                |

## 4 PROTOCOL APPROVAL SIGNATURES

### 4.1 Sponsor's Approval

This study will be performed in compliance with the final protocol or approved amendments, the current Helsinki Declaration, Good Clinical Practices (GCP) and applicable regulatory requirements.

Executive VP, Scientific and  
Medical Affairs

Jean-Jacques GARAUD, MD,  
INOTREM

janvier 17, 2022 | 5:30

DocuSigned by:  
PM CET  
*Jean-Jacques GARAUD*  
F94C059B3693400...

Date:

Signature:

Clinical Operations Director

Valérie CUVIER,  
INOTREM

janvier 17, 2022 | 5:32

DocuSigned by:  
PM CET  
*Valérie Cuvier*  
BE4A5F62AFEC414...

Date:

Signature:

Study Statistician

Jean-Marie GROUIN, PhD

janvier 18, 2022 | 12:49 AM PST

DocuSigned by:  
*Jean-Marie Grouin*  
1AB2A841022A421...

Date:

Signature:

## 4.2 Declaration of Coordinating Investigator

I hereby agree that I will assume the responsibilities of the Coordinating Investigator in this study, including reviewing and signing the following: study protocol, amendments to the protocol if applicable, and final study report.

Bruno FRANÇOIS, MD  
Study Coordinating Investigator

janvier 17, 2022 | 5:33 PM CET

Date:

DocuSigned by:



0B110DF6108A47D...

Signature:

### 4.3 Investigator's Agreement

I have read this Protocol No. MOT-C-203 sponsored by INOTREM SA.

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

I have fully discussed the objectives of this trial and the contents of this protocol with a representative of the sponsor.

I understand that the 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 trial, without written authorization from the sponsor. It is, however, permissible to provide information to a patient and/or legal representative in order to obtain consent.

I agree to conduct this trial according to this protocol and to comply with its requirements, ethical and patient safety considerations and guidelines, and to conduct the trial in accordance with ICH guidelines on GCP and with the applicable regulatory requirements.

I understand that the sponsor may decide to suspend or prematurely terminate the trial at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the trial I will communicate my intention immediately in writing to the sponsor.

\_\_\_\_\_  
Investigator (print name)

\_\_\_\_\_  
Date:

\_\_\_\_\_  
Signature:

## 5 STUDY PERSONNEL AND STUDY ADMINISTRATIVE STRUCTURE

|                                              |                                                                                                                                                                                                                                                                                                         |
|----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sponsor's Representative and Medical Officer | Jean-Jacques Garaud, MD<br>Executive VP, Scientific and Medical Affairs<br>Email: <a href="mailto:jjg@inotrem.com">jjg@inotrem.com</a><br>Tel: +33 6 30 62 86 51                                                                                                                                        |
| Sponsor's Main Contact                       | Valérie Cuvier<br>Clinical Operations Director<br>Email: <a href="mailto:vc@inotrem.com">vc@inotrem.com</a><br>Tel: +33 6 80 61 52 05                                                                                                                                                                   |
| Sponsor Site                                 | INOTREM SA<br>54 rue de Ponthieu<br>75008 Paris, France                                                                                                                                                                                                                                                 |
| Coordinating Investigator                    | Bruno François, MD<br>Réanimation Polyvalente & Inserm CIC 1435<br>CHU Dupuytren<br>2 Av Martin Luther King<br>87042 Limoges Cedex, France<br>Tel: +33(0)5 55 05 62 54<br>Fax: +33 (0)5 55 05 80 57<br>Email: <a href="mailto:bruno.francois@chu-limoges.fr">bruno.francois@chu-limoges.fr</a>          |
| Clinical Coordinating Center (CCC)           | <u>EU:</u><br>SLUCCC<br>Saint Luc Clinical Coordinating Center<br>Avenue Hippocrate 10<br>1200 Brussels, Belgium<br><br><u>US:</u><br>Ocean State Clinical Coordinating Center<br>1 Virginia Avenue, Suite 105<br>Providence, RI 02905<br><br>Contact details (phone and email) are provided separately |
| Study Statistician                           | Jean-Marie Grouin, PhD<br>One Minus Beta Biostatistics Consulting<br>72, rue du pré des Coulons<br>78810 Feucherolles, France<br>Tel: +33 (0) 631 444 042<br><a href="mailto:grouin2@wanadoo.fr">grouin2@wanadoo.fr</a>                                                                                 |

Pharmacovigilance Provider

Stragen Services SAS  
Bâtiment Le Quadrille 1  
19 rue Jacqueline Auriol  
69008 Lyon  
Tel: +33 4 78 42 95 26  
Fax: +33 4 78 42 55 71  
Mobile: + 33 6 22 35 68 20  
InotremPV@stragen.fr

IMP Management:

ABF Pharmaceutical Services GmbH  
Brunner Straße 63, 18-19  
1230 Vienna, Austria  
Mobile: +43 (0) 676 897 11 55 19  
Fax: +43 18901200-11  
amina.covic@abf-pharma.com

Monitoring, Data Management and  
Biostatistics

PPD France SAS  
27-35 Rue Victor Hugo  
94200 Ivry sur Seine - France  
Tel: +33 1 58 46 58 71  
Antoine.Nalpas@ppdi.com

The principles of the initial management bundle are to provide cardiorespiratory resuscitation and diminish the immediate danger of the underlying infection. Resuscitation involves intravenous fluids, vasopressors and mechanical ventilation where needed. The initial management of infection entails identifying the most likely source of infection, obtaining cultures, instigating empiric antimicrobial therapy and source control where appropriate. The

choice of empirical antibiotic treatment depends on the site of infection, the location the infection was acquired (e.g. community, nursing home or hospital), medical history, and local microbial susceptibility patterns.

Importantly, unlike other major illnesses, treatment for sepsis is nonspecific and restricted to support of failing organ functions. There are no approved drugs that specifically target septic shock. It is expected that septic shock will remain an important clinical problem in the future, caused by a combination of factors, including the ageing population, aggressive therapies for chronic diseases (in particular malignancies) and emerging antibiotic resistance. As such, there is an unmet clinical need for effective therapeutic interventions in septic shock.

### 6.3 Nangibotide for the Treatment of Septic Shock

The Triggering Receptor Expressed on Myeloid Cells 1 (TREM-1) is an immunomodulatory receptor expressed on innate immune cells, platelets and endothelial cells. The biological function of TREM-1 is the amplification of inflammation. In sepsis, this amplification may result in an exuberant and hyperactivated immune state ("genomic storm"), which is responsible for the onset and progression of the disease.

Nangibotide is a 12 amino-acid peptidic fragment derived from TREM-Like Transcript-1 (TLT-1), a receptor protein belonging to the TREM-1 family. Nangibotide can bind to ("trap") TREM-1 ligand and thereby modulate the amplification of the immune response caused by the activation of TREM-1 both in sepsis and myocardial infarction

TREM-1-induced activation of several intracellular proteins involved in inflammation as well as cytokine production in human neutrophils and monocytes was shown to be downmodulated by nangibotide *in vitro* in a dose dependent manner. In non-activated resting lymphocytes nangibotide does not modify several intracellular signaling pathways analyzed, including those involved in inflammation.

As septic shock is a life-threatening disease characterized by a dysregulated immune response, it is of paramount importance to consider the safety of nangibotide, when administered in a condition in which the immune system is activated. In every preclinical model of sepsis and septic shock studied, the administration of nangibotide was associated with protective effects especially on the degree of inflammation, cardiovascular system and survival.

In animal models of peritonitis (mouse and rat), a mortality of 90 to 95% was observed within 7 days following the onset of sepsis. The administration of nangibotide significantly decreased mortality and sepsis related symptoms, even when administered 24 hours after the initial injury. Inflammatory response markers were shown to be reduced, without completely abrogating them. Administration of nangibotide also resulted in reduction of sepsis-induced tissue abnormalities and showed protective effects on the cardiovascular system. In addition, the administration of nangibotide improved bacterial clearance in a mouse model of peritonitis. In a porcine model of peritonitis, nangibotide treatment led to a significant decrease of vasopressor (norepinephrine) administration which translated into a substantial protective effect of the cardiovascular system. Nangibotide also prevented sepsis-induced tissue abnormalities and dysfunctions in this model.

During an experimental monkey endotoxemia model, nangibotide attenuated the endotoxin-induced blood pressure decrease and release of several inflammatory cytokines in blood. In this model the cytokines IL-6, IL-8, TNF- $\alpha$ , CCL2, CCL3 and CCL4 were diminished to intermediate levels but not completely abrogated.

The rationale for taking this compound into further development is the expectation that it could be an effective new anti-sepsis therapeutic agent and the first causal treatment for septic shock.

Because of its mechanism of action, nangibotide may have an impact on the immune system, either on immune cells or on immune responses. Since nangibotide targets activated immune

cells in septic shock patients, the treatment with nangibotide may interfere with inflammatory/immune responses in an undesired way. However, in preclinical models, treatment with nangibotide resulted in a diminution of proinflammatory cytokine expression and concentration and not in a complete abrogation of cytokine responses. In addition, nangibotide treatment resulted in a better bacterial clearance in a polymicrobial sepsis murine model. Patients will be carefully monitored with laboratory analysis and changes in immune parameters will be followed. INOTREM is maintaining a risk management plan for the clinical development of nangibotide, which describes potential risks of nangibotide administration, their monitoring and measures for mitigation.

Other risks include infusion site associated reactions.

### 6.4.3 Benefit-Risk Assessment

The benefit risk ratio of the study design is considered favorable because:

- throughout the study, all patients receive standard therapy for the treatment of their septic shock
- the safety of study patients will be monitored by an independent Data Monitoring Committee (DMC) on an ongoing basis
- treatment with nangibotide has been shown to be safe and well tolerated in healthy volunteers and patients with septic shock
- patients may benefit from treatment with nangibotide

## 7 STUDY 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 soluble TREM-1 (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 (e.g. 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 utilization and post shock morbidity

### Exploratory

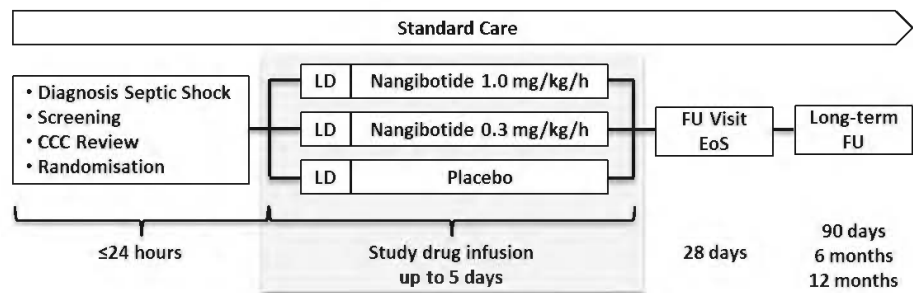
- To evaluate PK/PD relationship to nangibotide-mechanism-of-action-related markers

## 8 INVESTIGATIONAL PLAN

### 8.1 Overall Study Design and Plan Description

This is a randomized, double-blind, placebo-controlled dose-selection study in which two doses of nangibotide are tested versus placebo.





LD: Loading dose or matching placebo; FU: Follow-up; EoS: End of Study

Figure 1: Flow Chart

All assessments performed in the study are summarized in the study schedule provided in [Table 1](#) and [Table 2](#).

**Table 1: Study Schedule**

|                                               | SCR             |                    |                 |                 |                 |                 |                 |   |   | EoS             | FU unblinded <sup>2</sup> |           |            |
|-----------------------------------------------|-----------------|--------------------|-----------------|-----------------|-----------------|-----------------|-----------------|---|---|-----------------|---------------------------|-----------|------------|
| Assessment / Study Day <sup>1</sup>           | ≤24H            | 0                  | 1               | 2               | 3               | 4               | 5               | 6 | 7 | 28<br>+4d       | 90<br>±4d                 | 6m<br>±1w | 12m<br>±1w |
| Informed consent                              | X <sup>11</sup> |                    |                 |                 |                 |                 |                 |   |   |                 |                           |           |            |
| Inclusion/exclusion criteria                  | X               |                    |                 |                 |                 |                 |                 |   |   |                 |                           |           |            |
| Medical history and demographics              | X               |                    |                 |                 |                 |                 |                 |   |   |                 |                           |           |            |
| Previous therapies <sup>3</sup>               | X               |                    |                 |                 |                 |                 |                 |   |   |                 |                           |           |            |
| APACHE II Score                               | X               |                    |                 |                 |                 |                 |                 |   |   |                 |                           |           |            |
| Pregnancy test <sup>4</sup>                   | X               |                    |                 |                 |                 |                 |                 |   |   |                 |                           |           |            |
| Height and weight <sup>5</sup>                | X               |                    |                 |                 |                 |                 |                 |   |   |                 |                           |           |            |
| Physical Examination                          | X               |                    |                 |                 |                 |                 |                 |   |   | X <sup>14</sup> |                           |           |            |
| Vital Signs                                   | X               | X <sup>12</sup>    | X               | X               | X               | X               | X               |   |   | X               |                           |           |            |
| ECG                                           | X               | X <sup>12,15</sup> | X <sup>13</sup> | X <sup>13</sup> | X <sup>13</sup> | X <sup>13</sup> | X <sup>13</sup> |   |   | X               |                           |           |            |
| Organ dysfunction / SOFA Score <sup>6</sup>   | X               | X <sup>12</sup>    | X               | X               | X               | X               | X               | X | X |                 |                           |           |            |
| Charlson Comorbidity Index CCI)               | X               |                    |                 |                 |                 |                 |                 |   |   |                 |                           |           |            |
| Call to the CCC                               | X               |                    |                 |                 |                 |                 |                 |   |   |                 |                           |           |            |
| Randomization                                 | X               |                    |                 |                 |                 |                 |                 |   |   |                 |                           |           |            |
| Study Drug Infusion <sup>7</sup>              |                 | X                  | X               | X               | X               | X               | X               |   |   |                 |                           |           |            |
| Prior and concomitant Therapies               | X               | X                  | X               | X               | X               | X               | X               | X | X | X               |                           |           |            |
| Vasopressor                                   | X               | X                  | X               | X               | X               | X               | X               | X | X | X               |                           |           |            |
| IMV                                           | X               | X                  | X               | X               | X               | X               | X               | X | X | X               |                           |           |            |
| RRT                                           | X               | X                  | X               | X               | X               | X               | X               | X | X | X               |                           |           |            |
| Mortality                                     |                 | X                  | X               | X               | X               | X               | X               | X | X | X               | X                         | X         | X          |
| Adverse Events <sup>16</sup>                  | X               | X                  | X               | X               | X               | X               | X               | X | X | X               |                           |           |            |
| Clinical Laboratory (see table 2)             | X               | X <sup>12</sup>    | X               | X               | X               | X               | X               | X | X | X               |                           |           |            |
| Anti-drug antibodies (ADA)                    |                 | X <sup>12</sup>    |                 |                 |                 |                 |                 |   |   | X               |                           |           |            |
| PK <sup>17,18</sup> (see Table 2)             |                 | X <sup>12</sup>    | X <sup>13</sup> | X <sup>13</sup> | X <sup>13</sup> | X <sup>13</sup> | X <sup>13</sup> |   |   |                 |                           |           |            |
| Biomarker samples <sup>18</sup> (see table 2) |                 | X <sup>12</sup>    | X               | X               | X               | X               | X               | X | X | X               |                           |           |            |
| EuroQol (EQ 5D)                               |                 |                    |                 |                 |                 |                 |                 |   |   | X               | X                         | X         | X          |
| Healthcare resource utilization <sup>8</sup>  |                 |                    |                 |                 |                 |                 |                 |   |   | X               | X                         | X         | X          |
| Secondary infections <sup>9</sup>             |                 |                    |                 |                 |                 |                 |                 |   |   | X               |                           |           |            |
| Discharge letter collection <sup>10</sup>     |                 |                    |                 |                 |                 |                 |                 |   |   | X               |                           |           |            |

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

- 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 day28 as specified in [section 13.4](#)
- 17: PK sampling is optional as a sufficient number of samples have already been collected to support pharmacokinetic studies.
- 18: Certain exceptions are permissible for patients with concomitant Covid-19 diagnosis, see [section 12.19.6](#)

**Table 2: Laboratory Tests for Safety, Pharmacokinetics and -dynamics**

| Test                                                                                                                                                                                                                                                                  | Parameters                                                                                                                                                                                                         | Timepoints                                                                                                   |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| <b>Laboratory assessments for SOFA<sup>1</sup></b>                                                                                                                                                                                                                    | Bilirubin, platelets, creatinine, arterial blood gases                                                                                                                                                             | Daily until D7                                                                                               |
| <b>Chemistry<sup>1</sup></b>                                                                                                                                                                                                                                          | Aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, creatinine, urea, glucose, sodium, potassium, chloride, calcium, inorganic phosphate, total protein, albumin, lactate | Screening, baseline (D0), D1 to D5, D28 from routine laboratory assessments, first routine sample of the day |
| <b>Hematology<sup>1</sup></b>                                                                                                                                                                                                                                         | Hemoglobin, hematocrit, leucocytes, basophils, eosinophils, neutrophils, lymphocytes, monocytes, platelet count                                                                                                    | Screening, baseline (D0), D1 to D5, D28 from routine laboratory assessments, first routine sample of the day |
| <b>Coagulation<sup>1</sup></b>                                                                                                                                                                                                                                        | International Normalized Ratio (INR)                                                                                                                                                                               | Screening, baseline (D0), D1 to D5, D28 from routine laboratory assessments, first routine sample of the day |
| <b>Anti-drug antibodies<sup>2</sup></b>                                                                                                                                                                                                                               | Anti-drug antibodies                                                                                                                                                                                               | Baseline (pre-dose) and D28                                                                                  |
| <b>Cytokines, markers of vascular endothelium activation<sup>2</sup></b>                                                                                                                                                                                              | TNF $\alpha$ , IL-6, IL-10, CCL2 (MCP-1), procalcitonin, Ang-1, Ang-2                                                                                                                                              | Baseline (pre-dose), D1 to D5: daily                                                                         |
| <b>PK (Optional assessment)</b>                                                                                                                                                                                                                                       | Nangibotide circulating levels                                                                                                                                                                                     | Baseline (pre-dose), D1 to D5: daily until end of infusion<br>Within 3h after the end of the IMP infusion    |
| <b>sTREM-1 RUO/IUO<sup>2</sup></b>                                                                                                                                                                                                                                    | soluble TREM-1                                                                                                                                                                                                     | Baseline (pre-dose), D1 to D7: daily, D28                                                                    |
| <b>Blood samples for retention</b>                                                                                                                                                                                                                                    | Exploratory biomarkers<br><br>Exploratory transcriptomic biomarkers (PAXgene RNA)                                                                                                                                  | Baseline (pre-dose), D1 to D5: daily<br><br>Baseline (pre-dose), D2, D5 and D28                              |
| 1: Site; 2: Centralized, third party laboratory provider; RUO: research use only; IUO: Investigational Use Only; ICU: Intensive Care Unit<br>Certain exceptions are permissible for patients with concomitant Covid-19 diagnosis, see <a href="#">section 12.19.6</a> |                                                                                                                                                                                                                    |                                                                                                              |

- Health related quality of life (EQ 5D)
- Post shock morbidity
- Health care resource utilization

### 8.3 Adaptive Protocol Features

Some protocol features may be changed and are described in [Table 3](#).

**Table 3: Adaptive Protocol Features**

| Adaptive study design areas                                           | Features                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Limits                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Samples and assessments</b>                                        | <ul style="list-style-type: none"> <li>Timing of PK and/or biomarker samples may be adjusted in accordance with evolving data and dosing schedule</li> <li>Additional or less PK and/or biomarker samples may be taken in accordance with evolving data and dosing schedule</li> <li>Biomarker measurements may be added or removed in accordance with evolving data and dosing schedule</li> <li>Additional assessment dates (visits) may be added to the study schedule</li> <li>Assessments of health-related quality of life, resource use, hospitalizations and secondary infections may be added or removed.</li> <li>The method for obtaining long-term follow-up data may be switched from phone contact to mail or combined mail/phone</li> </ul> | <ul style="list-style-type: none"> <li>Minimum: sufficient PK samples according to the respective study objective</li> <li>Study specific maximum blood volume will not be exceeded</li> <li>Additional assessments (visits) will only be added while patients are still hospitalized. No additional patient visits to the hospital will be added</li> <li>No additional patient visits to the hospital will be added. No more than 4 follow-up assessments by phone or mail</li> </ul> |
| <b>Sample size</b>                                                    | <ul style="list-style-type: none"> <li>The sample size of the study may be increased or decreased according to the proportion of patients in the high sTREM-1 group after the interim analysis</li> <li>In case one treatment arm is stopped for futility, the remaining number of patients may be redistributed to the remaining treatment arms</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                | <ul style="list-style-type: none"> <li>Will be done only once after interim analysis</li> <li>The upper limit is an increase of 30% (135 patients)</li> </ul>                                                                                                                                                                                                                                                                                                                           |
| <b>Time window between onset of shock and initiation of treatment</b> | <ul style="list-style-type: none"> <li>The time window of 24 hours between onset of shock and start of study drug infusion may be shortened in accordance with evolving feasibility</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | <ul style="list-style-type: none"> <li>The allowed time will not be shorter than 12 hours</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Inclusion criteria: upper age limit</b>                            | <ul style="list-style-type: none"> <li>The number of elderly patients in a certain age range (e.g. &gt;80 and ≥85 years) may be capped</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <ul style="list-style-type: none"> <li>The cap should not exceed the proportion of patients in the total patient population</li> </ul>                                                                                                                                                                                                                                                                                                                                                  |
| <b>Responsibilities of the DMC</b>                                    | <ul style="list-style-type: none"> <li>Additional responsibilities may be added to the DMC</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <ul style="list-style-type: none"> <li>No DMC tasks specified in the study protocol will be removed</li> </ul>                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Responsibilities of the DAC</b>                                    | <ul style="list-style-type: none"> <li>The responsibilities of the DAC may be changed (addition or removal of tasks)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

| Timepoint                     | Data Requirements of Interim Analysis Report                                                                                                                                                                                                                      |
|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 112 (25%) randomized patients | <ul style="list-style-type: none"> <li>all adverse event data (including serious adverse events and deaths) data</li> <li>available PK data</li> <li>general study progress</li> </ul>                                                                            |
| 225 (50%) randomized patients | <ul style="list-style-type: none"> <li>all adverse event data (including serious adverse events and deaths) data</li> <li>available PK data</li> <li>data related to efficacy</li> <li>data related to sTREM-1 levels.</li> <li>general study progress</li> </ul> |
| Ongoing DMC meetings          | <ul style="list-style-type: none"> <li>Serious adverse events and deaths data</li> <li>general study progress</li> </ul>                                                                                                                                          |

These doses studied in the MOT-C-203 study have been covered in preclinical pharmacology and safety studies as well as clinical studies. Detailed summaries are available in the current version of the nangibotide investigator's brochure.

This study includes vulnerable patient populations. Patients with septic shock are unconscious or lack capacity to provide informed consent at the time of inclusion into the clinical trial. An emergency informed consent procedure will be applied according to applicable regulations and

according to the approval of the respective ethics committee (EC/) or institutional review board (IRB).

The incidence of septic shock does increase with age, therefore elderly patients aged 65 years and above (as defined in ICH E7) do represent a significant portion of patients with septic shock. Therefore, patients up to age of 85 years will be enrolled into the study.

## 9 SELECTION OF PATIENTS

### 9.1 Number and Source of Patients

A total of approximately 354 patients is planned in order to achieve 118 patients treated per arm.

Trial sites that are conducting more than one clinical trial competing for the same patient population should avoid a selection bias. Random allocation of patients with the diagnosis to the different trials is an acceptable method for the minimization of such bias and is recommended ([Ibrahim 2011](#)).

COVID-19: due to the COVID-19 pandemic, which has impacted the pace of enrollment, the trial will be stopped earlier with at least 354 evaluable patients (i.e., patients having completed the Day-28 assessment and with an available baseline sTREM-1 assessment).

### 9.2 Inclusion Criteria

To be eligible for the study, patients must present with a diagnosis of septic shock (according to Sepsis-3) and meet the following criteria:

1. Provide written informed consent (proxy/legal representative) according to local regulations
2. Age from 18 to 85 years (inclusive)

#### Sepsis

3. Documented or suspected infection: lung, abdominal or elderly urinary tract infection (UTI) in the elderly ( $\geq 65$  years)
4. Organ dysfunction defined as acute change in total SOFA score  $\geq 2$  points

#### Shock

5. Refractory hypotension requiring vasopressors to maintain MAP  $\geq 65$  mm Hg despite adequate volume resuscitation (as per recommendations of the Surviving Sepsis Campaign)
6. Hyperlactatemia (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

### 9.3 Exclusion Criteria

The presence of any of the following criteria will exclude a patient from study enrollment:

1. Previous episode of septic shock requiring vasopressor administration within current hospital stay
2. Underlying concurrent immunodepression with anti-CD52 alemtuzumab (Campath) or glucocorticoids  $> 75$  mg prednisone daily or equivalent for more than 7 days
3. Immunosuppressive therapy related to recent ( $< 6$  months) transplantation

4. Cancer chemotherapy (<3 months) implying an immunodepression
5. Known HIV infection with low CD4 cell count (<200) for at least 6 months
6. Known pregnancy (positive urine or serum pregnancy test)
7. Shock of any other cause, e.g. hypotension related to gastrointestinal bleeding
8. Ongoing documented or suspected endocarditis, history of prosthetic heart valves
9. Prolonged QT syndrome
10. End-stage neurological disease
11. End-stage cirrhosis (Child Pugh Class C)
12. Acute Physiology and Chronic Health Evaluation (APACHE) II score <15 or  $\geq 34$
13. Home oxygen therapy on a regular basis for > 6 h/day
14. Recent cardiopulmonary resuscitation (CPR) (within current hospital stay)
15. Body mass index (BMI)  $\geq 40$  kg/m<sup>2</sup> or weight  $\geq 130$  kg
16. Moribund patients
17. Decision to limit full care taken before obtaining informed consent
18. Participation in another interventional study in the 3 months prior to randomization

#### 9.4 Central Review of Patient Eligibility Prior to Inclusion

Before a patient can be included, the investigator or delegate must discuss the diagnosis of septic shock and other eligibility criteria by phone with the clinical coordinating center (CCC) of the study. Only patients approved by the CCC can be included in the study. The CCC will document all decisions in writing. The CCC operational procedures will be documented in a separate charter.

The CCC for the study is reachable by phone 24/7. The phone numbers and other contact details are provided in a separate document.

#### 9.5 Withdrawal of Patients

The investigator will withdraw a patient from the study (i.e. from any further study medication or study procedure) for one or more of the following reasons:

- At the request of the patient or legal representative (withdrawal of consent)
- If, in the investigator's opinion, continuation of the study would be detrimental to the patient's well-being
- If, in the opinion of the investigator or sponsor, the patient will require a concomitant medication representing a risk for the patient.
- Is withdrawn from the study upon the request of Sponsor, including if Sponsor terminates the study

As far as possible and depending on the reason and nature for withdrawal, all examinations scheduled by the study protocol should be completed. At least, examinations scheduled for day 28/EoS) must be performed on all patients who receive the investigational product but do not complete the study according to the protocol. In any case, the respective case report form (CRF)

section entitled “End of Study” on day 28 as well as survival status at day 90, 6 and 12 months must be completed.

In all cases, the reason for and date of withdrawal must be recorded in the CRF and in the patient’s medical records. The patient must be followed up to establish whether the reason was an AE, and, if so, this must be reported in accordance with the procedures in [section 13](#).

The investigator must make every effort to contact patients lost to follow-up. Attempts to contact such patients must be documented in the patient’s records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter). At least two documented attempts to contact the patient must be made before a patient can be considered lost to follow-up.

### **Withdrawal of Blood Samples from Future Analyses**

As stated in the informed consent form (ICF) and according to national provisions, the patient may request all previously retained identifiable samples to be destroyed.

## **9.6 Replacement of Patients**

Patients will not be replaced.

## **9.7 Patients of Reproductive Potential**

Since nangibotide is a peptide derived from an endogenous human protein, adverse effects to unborn offspring is considered unlikely. Since the testing of reproductive toxicity is not yet complete, the most stringent precautions for the inclusion of females of childbearing potential will be applied according to the guidance of the Clinical Trial Facilitation Group ([CTFG, 2014](#)). All female patients will have a serum or urine pregnancy test performed before enrollment into the study. Since the patients will be hospitalized in an ICU during treatment with study drug, contraceptive measures and additional pregnancy tests are not considered required. Since the half-life of nangibotide is very short (approx. 2 minutes), pregnancy testing beyond the stay in the ICU is not considered required.

# **10 STUDY AND CONCOMITANT TREATMENTS**

## **10.1 Investigational Medicinal Product (IMP)**

Nangibotide will be supplied as a stable lyophilized product in L50 type I glass vials containing 1200 or 400 mg of free base lyophilized LR12 peptide in sodium citrate and arginine buffer at pH 5.5. The powder is to be solubilized with water for injection to yield a clear and colorless solution of nangibotide. [Table 4](#) shows the composition of the IMP in vials and the concentration of each component as reconstituted solution. IMP will be stored under appropriate conditions in a reasonably secure +2 to +8°C refrigerator placed in a room of restricted access.

**Table 4: Composition of Nangibotide Drug Product**

| Product             | Function                                      | Quantity/Vial | Concentration after solubilization |
|---------------------|-----------------------------------------------|---------------|------------------------------------|
| <b>Low Dose</b>     |                                               |               |                                    |
| LR12                | Active pharmaceutical ingredient              | 400 mg        | 31 mg/mL (23 mM)                   |
| Trisodium citrate   | Buffer                                        | 103 mg        | 7.9 mg/mL (31 mM)                  |
| Arginine            | Solubilization & lyophilization bulking agent | 139 mg        | 10.7 mg/mL (62 mM)                 |
| HCl                 | pH adjustment                                 | q.s. pH 5.5   |                                    |
| Water for injection | Diluent for solubilization                    | 13 mL         |                                    |
| <b>High Dose</b>    |                                               |               |                                    |
| LR12                | Active pharmaceutical ingredient              | 1200 mg       | 92 mg/mL (69 mM)                   |
| Trisodium citrate   | Buffer                                        | 65 mg         | 5 mg/mL (17 mM)                    |
| Arginine            | Solubilization & lyophilization bulking agent | 331 mg        | 25.5 mg/mL (146 mM)                |
| HCl                 | pH adjustment                                 | q.s. pH 5.5   |                                    |
| Water for injection | Diluent for solubilization                    | 13 mL         |                                    |

## 10.2 Placebo

The placebo used in this study will be a lyophilized Arginine/Sodium Citrate buffer with the same appearance as the lyophilized drug product.

Table 5 shows the composition of the placebo in vials and the concentration of each component as reconstituted solution

**Table 5: Composition of Placebo**

| Product           | Function                                      | Quantity/Vial | Concentration after Solubilization |
|-------------------|-----------------------------------------------|---------------|------------------------------------|
| Trisodium citrate | Buffer                                        | 64 mg         | 4.9 mg/mL (19 mM)                  |
| Arginine          | Solubilization & lyophilization bulking agent | 628 mg        | 48.3 mg/mL (276 mM)                |
| HCl               | pH adjustment                                 | q.s. pH 5.5   |                                    |

## 10.3 Doses and Treatment Regimen

Patients will receive a CIV of nangibotide at 6.66 or 20 mg/kg/h loading dose for 15 minutes followed by a maintenance dose at 0.3 or 1.0 mg/kg/h or a matching placebo and 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). The patient weight at screening will be used for dose calculation throughout the treatment period. Patients must receive the study drug as continuous infusion without interruptions. In case of an interruption by accident or emergency, it should be resumed as quickly as possible without loading dose.

The patient whose treatment has been unblinded will continue in the study.

During screening for eligibility, before any study specific procedures are started, the investigator will obtain informed consent as specified in [section 16.2](#).

## 11.2 Screening / Pre-treatment Period

The purpose of the screening/ pre-treatment phase is to confirm patient eligibility for enrollment in the study based on the inclusion and exclusion criteria and to obtain written informed consent.

Patients who meet the following criteria:

- Provided informed consent
- all of the inclusion criteria and none of the exclusion criteria
- have been approved by the CCC

can be enrolled into the study.

**Note:** Before confirming the eligibility of a patient, adequate fluid therapy as recommended in the current guidance of the Surviving Sepsis Campaign should be applied (see [section 11.5.](#))

During the Screening/Pre-treatment period and after obtaining informed consent, the following assessments will be performed:

- Medical history and demographics
- Date of current hospital admission, ICU admission and initiation of IMV and RRT if applicable
- Time and details of fluid and vasopressor therapy
- Previous therapies (within 24 hours prior to IMP administration)
- APACHE II score
- Charlson Comorbidity Index (CCI)
- Serum or urine pregnancy test in all female patients of childbearing potential
- Physical examination
- Weight and height
- Vital signs
- ECG
- SOFA score
- Clinical laboratory (see [Table 2](#))
- Phone call with the CCC to approve patient inclusion in the study

## 11.3 Treatment Period (Day 0 to Day 5)

After meeting all eligibility criteria (confirmed by the CCC, see [section 9.4](#)), eligible patients will be randomized and treatment with study drug i.v. will be initiated

**Note:** Treatment with study drug must be initiated within 24 hours after the onset of septic shock, defined as the initiation of vasopressor therapy.

### 11.3.1 Baseline – Treatment Initiation (Day 0)

The following assessments will be performed at baseline:

- Confirmation of patient's eligibility (inclusion exclusion criteria)
- Confirmation of septic shock and time window for treatment initiation ( $\leq 24$  hours after onset)
- Randomization
- Concomitant therapy
- SOFA score
- Vital signs
- ECG

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). An interruption of vasopressor treatment of up to 6 hours is not considered vasopressor withdrawal). At the end of treatment, the i.v. infusion will be stopped. If feasible, one sample for PK assessment will be taken after the end of infusion (no later than 3 hours after).

The date of study completion or early withdrawal from study will be documented in the eCRF. In case of early withdrawal, the reason for withdrawal must be documented.

Norepinephrine (NE)/noradrenaline (NA) should be the first vasopressor initiated and a targeted MAP should be defined prior to IMP administration with 65 mmHg being the most classical target according to international recommendations. A different MAP target is acceptable, if pre-specified and deemed appropriate by the investigator for the clinical management of the patient

e.g. previous history of hypotension or hypertension. If a MAP of 65 mmHg cannot be achieved despite infusion of NE/NA, epinephrine/adrenaline, dopamine or vasopressin may be added. Phenylephrine should not be used except in the situations where (a) NE/NA or NE/NA and epinephrine/adrenaline/dopamine is associated with serious arrhythmias or (b) cardiac output is known to be high and blood pressure persistently low. Vasopressin must not be used as the initial vasopressor.

When sepsis is controlled and patient hemodynamically stable with a MAP above the pre-defined target, vasopressors infusion should be decreased and even weaned as soon as possible.

### 11.5.3 Invasive Mechanical Ventilation

All patients on mechanical ventilation will be screened daily for weaning readiness.

Each morning in accordance with local clinical practice, the delegated trial staff will evaluate and screen each patient receiving mechanical ventilation for suitability of a spontaneous breathing trial.

All of the following conditions must be met to proceed with a spontaneous breathing trial:

- Underlying sepsis under control / stable
- $\text{FiO}_2 \leq 40\%$  and positive end-expiratory pressure (PEEP)  $\leq 8$  cm H<sub>2</sub>O to maintain  $\text{SaO}_2 \geq 90\%$
- Hemodynamically stable
- Adequate cough.

If not all of the abovementioned conditions are met during the screening, current ventilation will be continued. The screening may be repeated any time of day and/or multiple times per day if a condition is not met during the morning screening.

Appropriate information will be documented in the patient's medical records and/or in the eCRF.

If the patient tolerates the spontaneous breathing trial for at least one hour, patient will be considered for extubation.

### 11.5.4 Sedation

Sedation recommendations will follow the Surviving Sepsis Campaign guideline and continuous or intermittent sedation should be minimized as much as possible in mechanically ventilated patients, targeting specific titration end points. A daily sedation interruption protocol may be applied; however, this is not mandatory and left to the decision of the investigator.

## 12 STUDY METHODOLOGY

### 12.1 Medical History

All relevant medical history (diagnoses) available from patient records will be collected in the eCRF.

### 12.2 Previous and Concomitant Therapies

All treatments taken by the patients prior to the study and at any time during the study in addition to the investigational product, are regarded as prior and concomitant treatments and must be documented on the appropriate pages of the eCRF. Refer to [section 10.7](#) for details.

### 12.2.1 Vasopressors

The use of vasopressors for the treatment of septic shock will be documented in the eCRF. The name (INN) and start and stop date and time will be recorded. In addition, the highest daily dose will be recorded until day 28. Vasopressor treatment for other reasons will be documented as concomitant medication.

### 12.2.2 Antibiotic Therapy

Details of antibiotic treatment will be collected in the eCRF until D28. Details of blood cultures and antibiogram will be collected in the eCRF.

## 12.3 APACHE II Score

The Acute Physiology and Chronic Health Evaluation II score is a severity-of-disease classification system ([Knaus 1985](#)). An integer score from 0 to 71 is computed based on measurements of:

- AaDO<sub>2</sub> or PaO<sub>2</sub> (depending on FiO<sub>2</sub>)
- Body temperature (see [section 12.5](#))
- Mean arterial pressure
- pH arterial
- Heart rate
- Respiratory rate
- Sodium (serum)
- Potassium (serum)
- Creatinine (serum). Value to be doubled in case of renal acute failure.
- Hematocrit
- White blood cell count
- Glasgow Coma Scale

Higher scores correspond to more severe disease and a higher risk of death.

Patients eligible for the study must not have an APACHE II score <15 or ≥ 34.

Details on data assessment and collection will be provided in a separate manual.

## 12.4 Charlson Comorbidity Index

The Charlson comorbidity index ([Charlson 1987](#)) predicts the one-year mortality for a patient who may have a range of comorbid conditions, such as heart disease, AIDS, or cancer (a total of 22 conditions). Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with each one. In addition to comorbid disease, a further score of one additional point is added for each decade over 50 years of age (maximum 4 points) in studies including long term follow up. Scores are summed to provide a total score which is used to calculate estimated mortality.

Clinical conditions and associated scores are as follows:

| Condition                                                                                                                                                                                              | Score (for each condition) |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| Myocardial infarct, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease, diabetes. | 1                          |
| Hemiplegia, moderate or severe kidney disease, diabetes with end organ damage, tumor, leukemia, lymphoma.                                                                                              | 2                          |
| Moderate or severe liver disease.                                                                                                                                                                      | 3                          |
| Malignant tumor, metastasis, AIDS                                                                                                                                                                      | 6                          |

## 12.5 Vital Signs

Systolic and diastolic blood pressure, heart rate and temperature will be documented in the eCRF.

For temperature, rectal or tympanic is preferred. In case a site cannot provide these measurements, bladder or axillary temperature is acceptable. A correction of +0.5 degree should be added to the axillary temperature.

## 12.6 SOFA Score

The SOFA (sequential organ failure assessment) score is a scoring system to determine the extent of a person's organ function or rate of failure. It is based on six different scores, one for each of the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems ([Vincent 1998](#)).

It will be calculated daily between screening and day 7. SOFA scores will be required, even in case of earlier discharge from the ICU. SOFA scores are defined according to the following:

### Respiratory System

| PaO <sub>2</sub> /FiO <sub>2</sub> (mmHg)                                                                                                              | SOFA Score |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| < 400                                                                                                                                                  | 1          |
| < 300                                                                                                                                                  | 2          |
| < 200 and with respiratory support                                                                                                                     | 3          |
| < 100 and with respiratory support                                                                                                                     | 4          |
| For timepoints where arterial blood gas value is not available, guidance for the estimation of PaO <sub>2</sub> and FiO <sub>2</sub> will be provided. |            |

### Nervous System

| Glasgow coma scale | SOFA Score |
|--------------------|------------|
| 13-14              | 1          |
| 10-12              | 2          |
| 6-9                | 3          |
| < 6                | 4          |

**Cardiovascular System**

| Mean arterial pressure OR administration of vasopressors required                                     | SOFA Score |
|-------------------------------------------------------------------------------------------------------|------------|
| MAP < 70 mm/Hg                                                                                        | 1          |
| dop ≤ 5 or dob (any dose)                                                                             | 2          |
| dop > 5 OR epi ≤ 0.1 OR nor ≤ 0.1                                                                     | 3          |
| dop > 15 OR epi > 0.1 OR nor > 0.1                                                                    | 4          |
| Doses are in µg/kg/min ; dop : dopamine ; dob : dobutamine ; epi : epinephrine ; nor : norepinephrine |            |

**Liver**

| Bilirubin (mg/dL) [µmol/L] | SOFA Score |
|----------------------------|------------|
| 1.2–1.9 [> 20-32]          | 1          |
| 2.0–5.9 [33-101]           | 2          |
| 6.0–11.9 [102-204]         | 3          |
| > 12.0 [> 204]             | 4          |

**Coagulation**

| Platelets×10 <sup>3</sup> /mL | SOFA Score |
|-------------------------------|------------|
| < 150                         | 1          |
| < 100                         | 2          |
| < 50                          | 3          |
| < 20                          | 4          |

**Kidneys**

| Creatinine (mg/L) [µmol/L]; urine output; renal replacement therapy    | SOFA Score |
|------------------------------------------------------------------------|------------|
| 1.2–1.9 [110-170]                                                      | 1          |
| 2.0–3.4 [171-299]                                                      | 2          |
| 3.5–4.9 [300-440] (or < 500 mL/d)                                      | 3          |
| > 5.0 [> 440]; urinary output < 200 ml/d; on renal replacement therapy | 4          |

In cases where the physiological parameters do not match any row, zero points are given. In cases where the physiological parameters match more than one row, the row with most points is picked.

Detailed instructions for the collection and calculation of SOFA score will be provided in a separate manual.

**12.7 Electrocardiographic (ECG) Measurements**

12-lead ECGs will be recorded at the time-points described in the study plan in [Table 1](#). The baseline ECG should be done in triplicate, at least 1 minute apart. ECG printouts or copies will be collected by the sponsor. Original printouts are preferred.

All ECGs will be subject to central overreading by independent cardiologists. The methodology and findings will be reported separately.

## 12.8 Physical Examination, Height and Weight

Physical examinations will be performed as detailed in the Study Plan ([Table 1](#)).

A full physical examination includes an assessment of the following: eyes, ears, nose, throat, cardiovascular, respiratory, musculoskeletal, venous system, gastro-intestinal, lymphatic, dermatological and neurological system.

A brief physical examination will be symptom oriented and will not include specific parameters of full physical examination.

Height and weight will be measured at screening only. It will be documented in centimeters and weight in kilograms respectively. The weight of the patient should be determined as accurate as reasonably feasible. In case a measurement of the patient's weight is not feasible, the best possible estimate should be used. The BMI will be calculated from the height and weight. The eCRF may allow for the collection of weight and height in local units, which then will be converted into SI units.

## 12.9 Invasive Mechanical Ventilation and Intubation

The beginning and end of each episode of IMV will be recorded. For each episode, start and stop date and time will be recorded in the eCRF from beginning of IMV to day 28.

Information will be collected in the eCRF on the following:

- Ventilation requiring tracheal intubation or tracheostomy
- Non-invasive ventilation (e.g. positive pressure, high flow)
- Extracorporeal respiratory support

## 12.10 Renal Replacement Therapy

The beginning and end of each episode of renal replacement therapy (RRT) will be recorded. For each episode, start and stop date and time will be recorded in the eCRF from beginning of RRT to day 28.

Continuous and intermittent renal replacement therapy will be considered a single episode of renal failure if the administrations are not separated by at least 5 days.

## 12.11 Sepsis Related Clinical Events

Clinical events related to septic shock or sepsis complications will be collected. The following events will be considered clinical events related to septic shock or sepsis complications:

- Death related to septic shock, that is, related to septic shock or a sequela of sepsis based on the interpretation of the investigator.
- Cardiovascular events: the need for vasoactive drugs, hypotension.
- Respiratory events: decreased PaO<sub>2</sub>/FiO<sub>2</sub>, mechanical ventilation, hypoxia, acute respiratory distress syndrome, acute lung injury, or respiratory failure.
- Hepatic events: hepatic injury or liver dysfunction that leads to an increase from baseline in the serum level of bilirubin or other liver function tests.
- Renal events: renal failure, renal insufficiency, or renal injury that leads to an increase from baseline in serum creatinine.
- Hematologic/coagulation events: coagulopathy, disseminated intravascular coagulation, thrombocytopenia, or thrombocytosis.
- Other septic shock related symptoms: tachypnea, hypopnea, leukocytosis, leukopenia, hypothermia, hyperthermia, tachycardia, or bradycardia.

The documents should be identified by patient number only and all information that can identify the patient must be removed before transmission to the sponsor.

## 12.18 Resource Utilization

The extent of healthcare resource utilization will be assessed at day 28, day 90 and after 6 and 12 months.

The assessments at day 28 include:

- Duration of ICU and overall hospital stay for the current episode of septic shock
- Discharge location:
  - Home with no support
  - Home with support (paid/unpaid)
  - Rehabilitation site
  - Nursing facility
  - Other hospital
  - Still in trial hospital or readmitted to trial hospital
  - Death
  - Unknown
- Rehospitalization

On day 90, 6 and 12 months the following information will be collected:

- Admission to hospitals
- duration of hospitalization, nature of hospital admission (ICU, surgery or medicine), discharge location
- Patient location:
  - Home with no support
  - Home with support (paid/unpaid)
  - Rehabilitation site
  - Nursing facility
  - Other hospital
  - Still in trial hospital or readmitted to trial hospital
  - Death
  - Unknown

## 12.19 Laboratory Tests

### 12.19.1 Local Laboratory Tests

The following laboratory tests will be performed at the clinical sites and the results will be transcribed into the clinical database.

#### Hematology, Chemistry and Coagulation

Assessments of hematology, chemistry and coagulation score will be performed according to [Table 2](#).

#### Pregnancy Test (Female Patients)

A serum or urine beta-human chorionic gonadotropin (HCG) pregnancy test will be performed on all women of childbearing potential prior to inclusion into the study.

### 12.19.2 Centralized Laboratory Tests

All centralized laboratory tests will be performed by a third-party provider and blood sampling procedures are described in detail in a separate laboratory manual.

## Biomarkers

Blood samples for the assessment of biomarkers will be collected throughout the study according to [Table 2](#). Details for sampling and processing requirements, storage and shipment to the respective laboratories are described in the laboratory manual.

## Pharmacokinetic (PK) Assessments

Venous blood samples for the determination of concentrations of nangibotide will be taken at the times presented in the Study Schedule ([Table 1](#) and [Table 2](#)). The date and time of collection will be recorded on the appropriate eCRF.

All sample handling procedures, including the time of each sample collection, the time of placement into frozen storage (at the end of the sample workup), will be documented in detail in the laboratory manual. The procedures and materials used, e.g. collection and storage tubes, were examined prior to any analytical measurements as part of the analytical method validation, to rule out any possible pre-analytical interference with the analyte.

PK sampling becomes optional as sufficient samples have been collected to support pharmacokinetic studies and in order to ease recruitment since the pharmacokinetic sampling procedure is technically difficult and not always easy to conduct at sites.

The presence of ADA will be assessed as described in [Table 1](#) and [Table 2](#). A venous blood sample will be collected for evaluation of anti-drug antibody presence for all patients at the selected time-points. Further details and sample processing will be described in the laboratory manual.

## Unused Blood Samples

Blood samples not used for scheduled laboratory test may be also used for exploratory analyses and will be treated as described in [section 12.19.5](#) below.

### 12.19.3 Blood Sample for Retention

Blood samples for future exploratory analyses of biomarkers as described in [Table 2](#) will be retained for all patients. The specimen will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy of nangibotide treatment, adverse events or disease progression
- To increase knowledge and understanding of the septic shock disease biology

All biomarker samples will be destroyed no later than 5 years after the Clinical study report has been completed. However, the storage period will be in accordance to the ICF approved by the ethics committee and applicable laws.

All biomarker specimens will be subject to the confidentiality standards described in [section 17.5](#).

### 12.19.4 Volume of Blood Sampling

The total blood volume sampled during the study in addition to standard care for each patient will be approximately 170 mL.

The total volume of blood that will be withdrawn from each patient in this study will be further specified in a separate manual. The actual amount withdrawn may be different per patient, as the assessments according to standard of care may vary, in case samples need to be repeated for technical reasons or in case of an adapted design of the study. The total blood volume sampled in addition to standard of care will not exceed 250 mL.

**Adverse event (AE):** Any untoward medical occurrence in a patient or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an

|             |                                                                                                                     |
|-------------|---------------------------------------------------------------------------------------------------------------------|
| <b>Mild</b> | No interference with the patient's daily activities and does not require mandatory corrective/symptomatic treatment |
|-------------|---------------------------------------------------------------------------------------------------------------------|

|                 |                                                                                                                                                           |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Moderate</b> | Moderate interference with the patient's daily activities and/or requires minimal medical intervention or corrective treatment required                   |
| <b>Severe</b>   | Major and unacceptable interference with the patient's daily activities and requires mandatory corrective/symptomatic treatment, possible hospitalization |

The investigator should use clinical judgment in assessing the intensity of events not directly experienced by the patient (e.g., laboratory abnormalities).

The causal relationship of AEs will be rated as either **related** (reasonable possibility) or **unrelated** (no reasonable possibility) to the IMP.

The causal relationship of a SAE to the IMP will be rated as follows:

|                  |                                                                                                                                                                                                                                                                                 |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Unrelated</b> | Clearly and incontrovertibly due only to extraneous causes, and does not meet criteria listed under unlikely, possible or probable.                                                                                                                                             |
| <b>Unlikely</b>  | Does not follow a reasonable temporal sequence from administration of the IMP or is most likely related to another etiology than the trial drug such as the patient's clinical state, environmental factors or other therapies.                                                 |
| <b>Possible</b>  | Follows a reasonable temporal sequence from administration of the IMP, and/or a causal relationship cannot be excluded and remains likely.                                                                                                                                      |
| <b>Probable</b>  | Good reason (such as clear-cut temporal association with improvement on cessation of the IMP or reduction in dose, or reappears upon (accidental) rechallenge, or follows a known pattern of response to the IMP) and sufficient documentation to assume a causal relationship. |

The action taken with the IMP for an AE will be rated as: product discontinued, dosing interrupted, none, not applicable. AEs requiring therapy will be treated with recognized standards of medical care to protect the health and the well-being of the patient.

The outcome of an AE will be rated as recovered, recovering, not recovered, recovered with sequelae, fatal or unknown. The investigator will follow up any AE until it is resolved or until the medical condition of the patient is stable. All relevant follow-up information will be collected. For AEs that are ongoing at the last visit, the investigator will make thorough efforts to document the outcome.

## 13.2 Serious Adverse Events (SAE)

### 13.2.1 Definitions

**Serious Adverse Event:** Any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly or birth defect

- Is an important medical event

**Death:** The death of a patient enrolled in a clinical study is per se not an event, but an outcome. Any AE resulting in a fatal outcome must be fully documented and reported, including situation for which the death occurred after treatment end, and regardless of the causality relationship between the death and the IMP. The cause of the death is usually the AE. If the cause cannot be determined, the case will be considered an unexplained death.

**Life-threatening:** Any AE that places the patient, in the view of the initial reporter (investigator), at immediate risk of death from the AE as it occurred, i.e. it does not include an AE that, had it occurred in a more severe form, might have caused death.

**Disability:** A substantial disruption of a person's ability to conduct normal life functions.

**Important medical event:** An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered as a SAE when, based upon appropriate medical judgement, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. The concept includes AEs which suggest a significant hazard, contraindication or precaution for use, occurrence of malignancy or development of drug dependency or drug abuse.

### 13.2.2 Other Events to be Treated as Serious Adverse Events

**Exposure to drug during pregnancy:** In principle, pregnancy and the lactation period are exclusion criteria for clinical studies involving investigational drugs, which are not directly related to the respective conditions. In the event of a pregnancy occurring during the course of this particular study (until day 28), the patient should be withdrawn from study, but closely followed-up during the entire course of the pregnancy and postpartum period.

### 13.2.3 Other Events to be Reported

**Investigational Medicinal Product (IMP) Overdosing:** An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the study protocol. For the purposes of this clinical trial, any dose of IMP administered to a patient that exceeds the dose or duration of treatment foreseen in the protocol by more than 25% should be reported to Stragen Services.

### 13.2.4 Reporting of Serious Adverse Events

If any SAE occurs, the investigator will take appropriate action immediately and will strive to identify the cause of the events.

SAEs will be notified by the Investigator to Stragen Services, acting on behalf of the Sponsor, as soon as possible, i.e. within 24 hours from first knowledge by capturing it in the eCRF. Stragen Services, acting on behalf of the Sponsor, will be notified via notification email (auto-notification process) that an SAE was submitted in the eCRF; they will acknowledge the receipt of the SAE in the eCRF and will confirm receipt of the SAE information to the investigational site within one working day.

In case the investigator does not receive the acknowledgment of receipt in the eCRF or in case of technical issues, the investigator shall contact Stragen Services by any means for ensuring the receipt of SAE information at the earliest opportunity:

E-mail: InotremPV@stragen.fr  
Phone: +33 (0) 4 78 42 95 26  
Fax : +33 (0) 4 78 42 55 71

Any follow-up information will be reported to Stragen Services as soon as it becomes known, with the same process and timelines as described here above for initial reports. Photocopies of results, consultant report(s), a summary of the outcome of the reaction and the Investigator's opinion of IMP relationship to the SAE will be provided, if and when available.

The Sponsor will also perform an evaluation of the seriousness, causality and expectedness of all SAEs. All SAEs judged by either the Investigator or the Sponsor as having a reasonable suspected causal relationship to an IMP (i.e. probably or possibly related) will qualify as serious adverse reactions. If the Sponsor disagrees with the Investigator's causality assessment, both the opinion of the Investigator and the Sponsor are provided with the report.

All reported SAEs will be included in the INOTREM SA pharmacovigilance database.

Suspected unexpected serious adverse reactions (SUSARs) are AEs which have a reasonable possibility to be related to an IMP and are both unexpected (i.e. the nature or severity is not expected from the information provided in the investigator's Brochure) and serious. SUSARs are subject to expedited reporting to the Competent Authorities and Ethics Committees.

SUSARs will be notified to the Competent Authorities and to the relevant ECs/IRBs within 7 (for fatal and life-threatening SUSARs) or 15 days (all other SUSARs) as per applicable laws and regulations. The decision on the reportability will be made by the sponsor. Specific requirement for France/ANSM: Fatal and life-threatening SUSARs will also lead to an additional immediate notification to ANSM.

Annual safety reporting to the Competent Authorities and the Ethics Committees will be in agreement with ICH guideline E2F "Note for guidance on development safety update reports (DSUR)".

In addition, any other safety issue which may alter the current benefit-risk assessment of the IMP will be reported by the Sponsor (or delegate) on an expedited basis to Health Authorities, Ethics Committees and the Investigators.

### 13.3 Recording of Adverse Events and Follow-Up

All (serious and non-serious) adverse events detected by the Investigator or delegates, or spontaneously notified by the patient at each visit/examination must be reported on the respective section of the eCRF.

The following information should be reported for each adverse event, whether or not it can be attributed to trial drug:

- description of adverse event
- date of onset/date of disappearance
- characteristics of the event (seriousness, intensity)
- actions taken (with regard to study drug or treatment with concomitant medication required) must be reported in the CRF)
- outcome
- relationship with trial drug (causality assessment) and/or study participation

**All adverse events must be documented and followed up until the event is either resolved or a satisfactory explanation is found, or the investigator considers it medically justifiable to terminate the follow-up.**

Any AEs that are unresolved at the patient's last AE assessment in the study (i.e. at the end of study visit) are to be followed up by the Investigator for as long as medically indicated. INOTREM SA retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.





2. Two comparisons vs placebo: nangibotide 0.3 mg/kg/h vs placebo and nangibotide 1 mg/kg/h vs placebo.

A sequentially rejective test procedure based on the closed test principle using a graphical approach ([Bretz 2011](#)) that controls the family wise 1-sided error rate at 0.025 will be proposed : the initial 1-sided alpha levels will be 0.02 for the subgroup analysis and 0.005 for the overall population analysis. The transition matrix G (alpha propagation) and the algorithm will be prespecified and further detailed in the SAP before the unblinding of the database.

### 15.5 Missing Data and Intercurrent Events

With regard to the primary endpoint, most missing data occurring prior day 5 are expected to be related to the occurrence of death.

The primary method for handling missing data will apply the following rules:

- Missing values related to death occurring prior to day 5 are missing not at random (MNAR) and will be replaced by a penalty score of 4 points
- Missing values not related to death will be replaced by the last available post-randomization value of the SOFA score, i.e. based on the last observation carried forward (LOCF) method.

Additional sensitivity methods for handling missing data (LOCF method applied to all missing values whichever cause, multiple imputation-based methods, etc) will be further detailed in the SAP.

For other endpoints, methods for handling missing data will be further detailed in the SAP.

### 15.6 Analysis Sets

- **All randomized patients set (intent-to-treat, ITT set):** All patients who are randomized into the study and considered as randomized, i.e. with study drug assignments designated according to initial randomization, regardless of whether subjects received what was assigned.
- **Modified intent-to-treat (mITT) set:** All randomized patients having received at least one dose of the prescription of study drug (either nangibotide or placebo). Patients will be assigned to the treatment group as randomized (i.e. with study drug assignments designated according to initial randomization, regardless of whether subjects received what was assigned). The mITT set will be considered as the primary set for efficacy analyses.
- **Per protocol (PP) set:** All mITT patients without any major protocol deviation. Major protocol deviations will be identified during data review meetings that will be held before unblinding and database lock.
- **Safety set:** All enrolled patients having received at least one dose of the prescription of study medication (either nangibotide or placebo). The Safety set will be the basis for safety analyses. Patients will be assigned to the treatment group as treated for the Safety set.

### 15.7 Efficacy Analyses

#### 15.7.1 Primary Endpoint

The primary efficacy variable is the change of SOFA from baseline to day 5, which will be primarily analyzed on the modified ITT Set

The primary efficacy endpoint will be tested in the subgroup defined by patients with elevated sTREM-1 baseline levels and in the overall population.

Missing values related to death occurring prior to day 5 are missing not at random (MNAR) and will be replaced by a penalty score of 4 points and missing values not related to death will be replaced by the last available post-randomization value of the SOFA score, i.e. based on the last observation carried forward (LOCF) method.

The analysis of the change of SOFA score from baseline to day 5 will be based on an ANCOVA model adjusting for randomized treatment (placebo and nangibotide doses) and the baseline SOFA score. The LS Mean change of SOFA for each treatment (placebo or nangibotide doses) and the difference in LS Means between placebo and the nangibotide doses will be estimated in this model along with their 95% CIs. The validity of the model fitted will be checked (plot of studentized residuals against predicted values, etc.).

Additional sensitivity methods for handling missing data will be further detailed in the SAP.

The same analyses will be repeated on the PP set.

#### Subgroup Analyses:

The primary endpoint will be assessed in different subgroups of interest: age, sex, country, glucocorticoid use at ICU entry, baseline SOFA levels, baseline APACHE levels, baseline sTREM-1 levels, type of infection, appropriateness of antibiotic therapy and time from onset of septic shock to administration of IMP. Least square means and their 95% CI, as well as the p-values of the interaction tests will be presented on a forest plot.

### **15.7.2 Secondary Efficacy Endpoints**

Full details for the analysis of secondary endpoints ([section 8.2](#)) will be provided in the SAP.

#### **15.7.2.1 Key Secondary Endpoint**

All-cause mortality at day 28 will be analyzed as the key secondary endpoint. The all-cause mortality at day 28 will be analyzed in a logistic regression model adjusting for the same covariates used for the primary endpoint analysis. The treatment effect comparing each dose vs placebo will be estimated in terms of an odds ratio associated with the 95% CI and p-value.

#### **15.7.2.2 Overall Survival and Septic Shock Related Mortality**

Overall Survival will be defined as time from the date of randomization to the date of death (all causes). Patients without documentation of death at the time of analysis will be censored at the date last known to be alive.

The Kaplan-Meier (KM) survival curves will be provided. Survival K-M estimates with their 95% CI will be provided for each group on D5, D28, D90, at 6 months and 1 year.

KM survival medians (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group.

A log-rank test will be used 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 comparing the nangibotide doses vs placebo in terms of a hazard ratio with the 95% CI and p-value.

The septic shock related overall survival and mortality at day 28 will be analyzed with the same approach for the analysis of the All-Cause mortality at day 28.

### 15.7.2.3 Other Secondary Endpoints

Usual statistics will be used for the analysis of the other secondary endpoints ([section 8.2](#)). Details will be provided in the SAP.

## 15.8 Safety Analyses

Descriptive statistics will be used and detailed in the SAP to analyze the Safety Parameters as follows:

- Vital signs: SBP and DBP blood pressure, heart rate, and body temperature
- ECG (12-lead ECG)
- Safety laboratory tests: hematology, coagulation, plasma biochemistry.
- Presence of anti-nangibotide antibodies
- Adverse events, SAEs and deaths.

## 15.9 Pharmacokinetics, Pharmacodynamics and Pharmacoeconomic Analyses

Descriptive statistics will be used and detailed in a separate SAP for pharmacokinetic, pharmacodynamic and pharmacoeconomic endpoints ([section 8.2](#)).

### 15.10 Determination of the Optimal Baseline sTREM-1 Cut-off

Exploratory analyses based on the current study will be conducted to confirm the optimality of the cut-off chosen a priori for the subgroup analysis.

Methods for the determination of the optimal cut-off will be detailed in the SAP.

### 15.11 Sample Size Determination

A total of approximately 450 patients is planned in order to achieve 150 patients treated per arm.

The sample size determination is based on the primary endpoint, i.e. the change of SOFA score from baseline to day 5, tested in the subgroup of patients with elevated sTREM-1 levels (i.e.  $\geq 400$  pg/mL) and in the overall population.

Results from a previous phase 2 unpublished study (MOT-C-201) have shown that a difference of around 2 vs placebo in mean changes of the primary endpoint and a standard deviation of around 3.3, i.e. a standardized effect of 0.59 could be expected in the overall population. An even larger standardized effect could be expected in the subgroup of patients with elevated sTREM-1 levels.

It is also expected that the subgroup will comprise at least half the patients enrolled (around 225 patients) in the study.

Simulations to determine the sample size were performed considering a scenario of an expected difference of 2 versus placebo for one dose and a difference of 1.15 vs placebo for the other dose, a standard deviation of 3.3 and a 1-sided alpha level of 0.025. Considering 450 patients treated in the study with an expected 50% of patients in the high sTREM-1 group, the power achieved with this scenario is at least 90% for the claim of at least one dose in the subgroup of patients with elevated sTREM-1 levels and for the claim of at least one dose in the overall population. Of note, based on a conservative procedure (i.e. the Bonferroni approach) to account for comparison multiplicity (subgroup and overall population analyses and both doses vs placebo comparisons) the power is still maintained at  $\geq 90\%$ .

At the interim analysis (225 patients), the sample size may be increased to maintain the power of the pairwise comparisons of nangibotide vs placebo in the subgroup of patients with elevated sTREM-1 baseline levels (i.e.  $\geq 400$  pg/mL) if the proportion of patients with elevated sTREM-1 baseline levels in the interim sample is lower than 50%. The maximum possible increase in sample size will be 30% (135 additional patients).

The COVID-19 pandemic has impacted the pace of enrollment of the ASTONISH clinical trial. While the duration of the trial was planned to be 15 months with 450 patients randomized, the projected duration of the trial at the date of the amendment to protocol version 4.0 might now exceed 40 months, i.e. a more than 2.5 fold increase in the planned duration.

Whilst the ASTONISH enrollment rate was lower than expected due to the COVID-19 pandemic, the presence of a higher than expected proportion of high soluble TREM-1 patients in the study population at the interim futility analysis means that the amendment to protocol version 5.0 aims to stop the trial with at least 354 evaluable patients, i.e. patients having completed the day-28 assessment and with an available sTREM-1 baseline level, instead of the planned 450 patients.

This decrease in the initially planned number of patients **is not likely to** affect the planned power of the subgroup analysis if an early stop is planned with at least 354 evaluable patients. Actually, despite this early stop due to the COVID-19 and given an estimated interim proportion of patients with high **sTREM-1 baseline levels** higher than expected (around 70% compared to 50% initially expected), the power of the subgroup analysis will be maintained at a level as high as planned with the same assumptions considered for the initial sample size determination.

There is a decrease in power associated with the analysis in the overall population with fewer patients than planned, i.e. at least **354** evaluable patients instead of 450. However, again with the same assumptions considered for the initial sample size determination, the power of the overall analysis achieved with at least 354 evaluable patients is maintained above 90%.

### 15.12 Interim Analysis for Futility

An interim analysis will be performed on unblinded data and reviewed the DMC when about 225 patients have completed the 7-day period after randomization.

This interim analysis aims to:

- Perform a futility analysis for possibly dropping futile doses. The futility analysis will be performed on the primary endpoint. As a general rule, a dose will be considered futile if both standardized differences between the dose of nangibotide and placebo estimated in the subgroup and in the overall population are lower than 15%. However, decision rules for declaring a dose as futile will be further detailed in the DMC charter and other endpoints (mortality, safety endpoints, etc.) will also be taken into consideration for the final decision. The study will stop if both doses are considered futile at the end of stage 1.
- Possibly increase the sample size of the trial to maintain the power of the pairwise comparisons of nangibotide vs placebo in the subgroup of patients with elevated sTREM-1 baseline levels (i.e.  $\geq 400$  pg/mL) if the proportion of patients with elevated sTREM-1 baseline levels in the interim sample is lower than 50%.

In addition, after the first 112 (25%) and 225 (50%) patients have completed the 7-day period after randomization, unblinded interim analyses of safety will be performed and the data reviewed by the DMC (for details see [section 8.5](#)).

## 16 ETHICAL AND LEGAL ASPECTS

### 16.1 Good Clinical Practice (GCP)

This protocol complies with the principles of good clinical practice (ICH E6 R2), the principles of the World Medical Assembly (Helsinki 1964) and subsequent amendments ([WMA 2013](#)) and in keeping with local regulations.

### 16.2 Informed Consent

The informed consent is a process by which a patient voluntarily confirms his/her willingness to participate in a clinical study. It is the responsibility of the investigator or delegate to obtain valid informed consent from patients. All consent documentation must be in accordance with applicable regulations and GCP. Each patient is requested to sign the Informed Consent Form (ICF) after they have received and read the written patient information and received an explanation of what the study involves, including but not limited to the objectives, potential benefits and risk, inconveniences, and the patient's rights and responsibilities. Completed ICFs must remain on file and must be available for verification by Study Monitors at any time. Another original of the ICF must be given to the patient or the patient's legally authorized representative.

In case of incapacitated patients, the following procedures will be followed for obtaining informed consent according to applicable regulations:

- Informed consent will be obtained from the patient's family or legal representative as per local regulations
- If the family cannot be reached, an emergency informed consent procedure will be followed according local regulations.
- As soon a patient is no longer incapacitated, informed consent to continue participation will be obtained from the patient at that time.

The sponsor will be provided with a copy of the EC/IRB approved consent forms, and a copy of the EC/IRB written approval, prior to the start of the study.

### 16.3 Study Protocol Amendments

Any variation in procedure from that specified in the final clinical study protocol may lead to the results of the clinical study being questioned and, in some cases, rejected. Any proposed clinical study protocol change must therefore be discussed and approved with/by the Sponsor and submitted for EC/IRB and regulatory authority approval as specified below. Any relevant clinical study protocol change should be documented in a clinical study protocol amendment. Once the study has started, amendments should be made only in exceptional cases.

### 16.4 Approval of the Clinical Study Protocol and Amendments

Before the start of the study, the clinical study protocol, patient information leaflet and informed consent form, and any other appropriate documents will be submitted to the EC/IRB and to the respective Competent Authorities (CAs) and any other bodies involved in the review of the clinical trial, in accordance with local legal requirements. As required by local regulation or by the EC/IRB, the sponsor or investigator will also submit the financial arrangements for the study or other financial interests of the investigator in the investigational drug or Sponsor company to the EC/IRB.

Before the first patient is enrolled in the study, all ethical and legal requirements must be met.

If applicable, the EC/IRB and CAs must be informed of all subsequent amendments and administrative changes, in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the patient information leaflet and informed consent form should also be revised.

The (coordinating) investigator or sponsor's delegate must keep a record of all communication with the ECs/IRBs. This also applies to any communication between the (coordinating) investigator or sponsor's delegate and the authorities.

### **16.5 Ongoing Information for ECs/IRBs**

Unless otherwise instructed by the EC/IRB or local law, the sponsor or the investigator must submit to the EC:

- Information on SUSAR's from the investigator's site and other sites as required, as soon as possible and within the legal timelines
- Expedited safety reports from the Sponsor, as soon as possible
- Periodic reports on the progress of the study, where required
- Deviations from the protocol, where required

### **16.6 Protocol Adherence and Delegation of Duties**

The investigator and delegates must adhere to the study protocol. The investigator will be responsible for enrolling only those patients who have met the eligibility criteria of the study protocol. The investigator will be required to sign an Investigator Agreement to confirm acceptance and willingness for themselves and delegates to comply with the study protocol.

The investigator must ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments and their trial-related duties and functions. The investigator should maintain a list of subinvestigators and other appropriately qualified persons, to whom significant trial related duties were delegated.

### **16.7 Liability and Insurance**

The sponsor will maintain liability and insurance provisions for patients and investigators according to legal requirements and applicable regulations. These are available in separate agreements.

### **16.8 Discontinuation of the Study**

The study must be discontinued at the site on completion.

The whole study may be discontinued in the event of any of the following:

- Determination of unexpected, significant, or unacceptable risk to patients
- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients
- Plans to modify, suspend, or discontinue the development of the study drug

Completion or premature termination of the study will be reported by the Sponsor to the CAs and by the Sponsor or investigator to the EC/IRB as required by local regulation or by the EC/IRB.

Furthermore, the Sponsor or the investigator has the right to close the study site at any time. As far as possible, premature discontinuation should occur after mutual consultation.

Study materials must be returned, disposed of or retained as directed by the Sponsor.

## 16.9 Record Retention

The investigator must obtain approval in writing from the Sponsor before destruction of any records and must document any change of ownership.

Study records should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained. Patient identification codes must be retained according to ICH GCP or for at least 15 years after the completion or discontinuation of the trial whatever is the longest period in time.

If an investigator leaves an investigational site, the responsibility for archiving of all study related records must be transferred to another person (e.g. other investigator). The Sponsor must be informed about any change in responsibility.

## 17 DOCUMENTATION AND USE OF STUDY FINDINGS

### 17.1 Case Report Forms

An eCRF for the study will be available online, on a secure website. Only the investigators, or the sub-investigators/designee, are authorized to enter data in the eCRF. At the beginning of the study, a login will be allocated to each site staff who will be asked to identify himself/herself by a personal password.

The investigator, the sub-investigator or its designated representative will create a new eCRF for each patient having signed the informed consent.

In cases where data, already entered, requires correction, the initial value, the identity of the person who modify the data, the date and the reason of the modification are tracked in the audit trail of the eCRF.

Where applicable, the investigator will maintain complete and accurate paper format study documentation in a separate file. This may include information defined as “source data”, records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/sponsor, screening information, CRFs, SAE reports, laboratory reports and data clarifications.

### 17.2 Clinical Database

The eCRF data entry screens and database will be created using Medidata RAVE.

The eCRF application will be accessible by connecting on a dedicated and secure website. Each user will connect by using a personal identifier/password. The investigator, sub-investigators or designated representative will enter the data for each patient into the online eCRF application.

A Data Validation Manual (DVM) will describe the various data management processes required for the conduct of the study data cleaning.

Programmed consistency checks are defined in the electronic edit check specification. These checks will result in the production of electronic data queries. Listings for manual review will be programmed and any data queries will be raised manually into the RAVE database. The

Patients in this study will be known by a unique number. The results of this study containing the unique number and relevant medical information including ethnicity may be recorded and transferred to and used in other countries throughout the world, which may not afford the same level of protection that applies within the EU. The purpose of any such transfer would be to support regulatory submissions made by the sponsor in such countries.

## 17.6 Data Safety

The sponsor will ensure that appropriate data safety provisions are in place for the protection of patient data. This includes, but is not limited to the following:

- Access of data only permitted to authorized and trained individuals
- Computerized systems shall be suitable for the purpose and have controlled access and backup and disaster recovery mechanisms in place.
- Data will be collected and stored only to the extent required for the purpose of the study and the development and registration of nangibotide as drug. The storage duration is determined by applicable guidelines and regulations and long-term storage up to 25 years may be required.

## 17.7 Data Access, Portability and Removal of Individual Data

The sponsor does recognize the study patients' rights to access and obtain their personal data or have their personal data transferred as specified in the European Directive 95/46/EC (General Data Protection Regulation) or other applicable local regulation.

Prior to the study and data collection, all study patients will need to provide informed consent as required by the study protocol via a process approved by the responsible ethics committee. In case a patient withdraws his informed consent, the sponsor will honour requests for the removal or deletion of individual data where reasonably feasible.

Since the sponsor or the contracted CRO will not be collecting any data allowing the identification of an individual patient, any such request will be handled via the concerned investigator of the study.

## 17.8 Data Collection and Transfer of Study Data to Third Parties or Foreign Countries

During the course of the clinical trial, patient data collected via in the eCRF and transferred to the study database is being handled by a CRO on their IT systems. All data is being handled according to the CRO's data security and privacy procedures. The sponsor is monitoring the compliance of the CRO on an ongoing basis via a process defined in an internal SOP.

The sponsor intends to utilize the data from this clinical trial - if successful - for the registration of nangibotide as treatment for septic shock or other 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.

None of the patient data collected or transferred will contain any information that will allow to reveal the identity of individual patients, as no personal identifiers are collected.

## 17.9 Incidental Findings

The sponsor does not systemically assess individual patient data for incidental findings (previously undiagnosed medical or psychiatric conditions that are discovered unintentionally and during the evaluation of study data).

However, in case an incidental finding should occur, the sponsor will inform the respective investigator, who was responsible for the treatment of the respective patient.

## 17.10 Publications

INOTREM is dedicated to support free exchange of relevant scientific information. The study will be registered in a public clinical trial database. By signing the final protocol, the principal

investigator agrees to keep all information and results concerning the study and the investigational product confidential as long as the data remain unpublished. The Sponsor will document the results of the clinical trial in a study report. Prior to any submission, all manuscripts/abstracts must be presented to the Sponsor for possible comments.

If requested, the investigator will withhold publication to allow for filing a patent application or taking such other measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

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