AMENDED CLINICAL STUDY PROTOCOL

Applicable for Sites in France only

Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of 3 Doses of MOTREM in Patients with Septic Shock.

A Randomised, Double-blind, Two-Stage, Placebo Controlled Study

Test Product:	MOTREM (LR12)
Sponsor:	INOTREM S.A. 114 Rue La Boétie 75008 Paris France
Sponsor's Medical Officer:	Jean-Jacques Garaud, MD
Sponsor Protocol Number:	MOT-C-201
EudraCT Number:	2016-005032-14
Development Phase:	IIa
Coordinating Investigator:	Bruno François, MD
Version:	4.1
Date:	15 January 2019

1 STUDY SYNOPSIS

Protocol No.: MOT-C-201	**Study Drug:** MOTREM (LR12)

Coodinating Investigator:
Bruno François, MD ; Inserm 1435 Clinical Investigational Center

Title of the Study:
Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of 3 Doses of MOTREM in Patients with Septic Shock. A Randomised, Double-blind, Two-Stage, Placebo Controlled Study

Study Centre(s):
Multi-centre, multi-national study, refer to separate list in study file

Study Period (planned):	**Development Phase:**
• First patient first visit: Q2/2017 • Last patient last visit: Q2/2018	Clinical Phase IIa

Objectives:

Primary

- To evaluate the safety and tolerability of MOTREM in patients with septic shock

Secondary

- To evaluate the effects of MOTREM exposure over up to 5 days in patients with septic shock
- To evaluate the PK/PD and dose/PD relationship to TREM-1 pathway related markers
- To evaluate the effect of MOTREM on transcriptomics
- To evaluate the effect of MOTREM on clinical parameters (e.g. vasopressor doses, vasopressor-free days, ventilator-free days, mortality)

Methodology

This is a randomised, double-blind, two-stage, placebo controlled study. It consists of 2 stages with a similar treatment regimen, in which 0.3, 1.0 or 3.0 mg/kg/h of MOTREM is tested versus placebo.

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 undergo standard care management procedures.

After screening for eligibility, patients will be randomised to one of the treatment arms. They will then either receive a 5 mg/kg loading dose of MOTREM over 15 minutes followed by a continuous i.v. infusion of MOTREM or a matching placebo on top of standard of care.

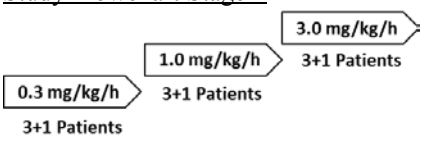
Treatment with study drug must be initiated as early as possible, but no later than 24 hours after the onset of septic shock, defined by the start of vasopressor therapy. Blood samples for the determination of MOTREM (LR12) plasma concentrations and exploratory pharmacodynamic analyses will be collected before and throughout the treatment period.

Patients will be treated until 12 (±2) hours after the resolution of their septic shock (defined as vasopressor withdrawal) with a maximum treatment duration of 5 days (120 hours).

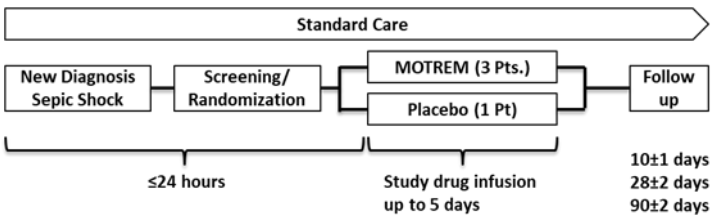
The survival status of patients after 28 and 90 days will be collected.

Stage 1 is investigating multiple ascending doses of MOTREM or placebo in a sequential design in cohorts of 4 patients (3:1 randomisation). After completion of a cohort (for up to 5 days of infusion), safety and PK data will be reviewed by an independent data safety monitoring board (DSMB) and the study will progress to the next cohort/stage.

Study Flowchart Stage 1

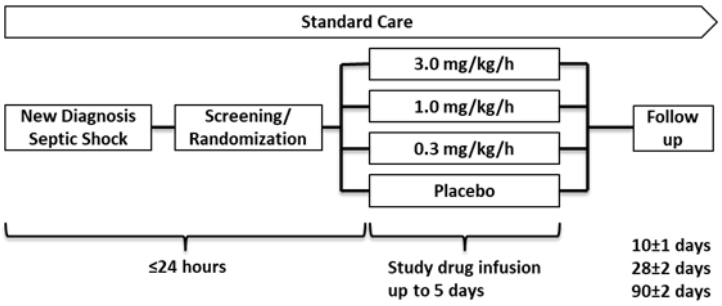


Per Cohort



Stage 2 investigates 3 doses of MOTREM in a randomised, balanced, parallel-group design involving up to 3 doses of MOTREM and a placebo arm. Only dose arms of MOTREM considered to be safe and well tolerated during Stage 1 will be administered in Stage 2.

Study Flowchart Stage 2



Number of Patients

The total planned number of patients is 48: twelve (12) patients in stage 1 and 36 patients in stage 2. The cohorts in stage 1 may be repeated according to the adaptive features of the study protocol. The total number of patients will not exceed 66 patients.

Diagnosis and Main Criteria for Inclusion

Diagnosis: Septic Shock (according to Sepsis-3)

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 80 years

Sepsis

3. Documented or suspected infection: lung, abdominal or elderly UTI (≥65 years)
4. Organ dysfunction defined as acute change in SOFA score ≥ 2 points

Shock

5. Refractory hypotension requiring vasopressors to maintain MAP ≥65mm Hg despite adequate volume resuscitation of at least 20 ml/kg within 6 hours
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 will exclude a patient from study enrolment:

1. Previous episode of septic shock (vasopressor administration) within current hospital stay
2. Underlying concurrent immunodepression (specified in appendix 2)
3. Solid organ transplant requiring immunosuppressive therapy
4. Known pregnancy (positive serum pregnancy test)
5. Prolonged QT syndrome (QTc ≥ 440 ms)
6. Shock of any other cause, e.g. hypotension related to gastrointestinal bleeding
7. Ongoing documented or suspected endocarditis, history of prosthetic heart valves
8. End-stage neurological disease
9. End-stage cirrhosis (Child Pugh Class C)
10. Acute Physiology And Chronic Health Evaluation (APACHE) II score ≥ 34
11. End stage chronic renal disease requiring chronic dialysis
12. Home oxygen therapy on a regular basis for > 6 h/day
13. Severe obesity (BMI ≥ 40)
14. Recent CPR (within current hospital stay)
15. Moribund patients
16. Decision to limit full care taken before obtaining informed consent
17. Participation in another interventional study in the 3 months prior to randomisation
18. APACHE II score <14

Test Product, Dose and Mode of Administration

MOTREM (LR12) will be administered as continuous i.v. infusion for up to 5 days. The doses administered are as follows:

Dose level	i.v. loading dose T = 15'	Maintenance i.v. dose T = up to 120 (±2) h
	[mg/kg]	[mg/kg/h]
Dose level 1	5.0	0.3
Dose level 2	5.0	1.0
Dose level 3	5.0	3.0

Reference Product, Dose and Mode of Administration

Matching placebo (saline without MOTREM)

Duration of Treatment

Study drug will be administered until 12 (±2) hours after the resolution of shock (vasopressor cessation) for a maximum of five (5) days.

Duration of Clinical Study

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

Duration of follow-up: up to 90 days

Criteria for Evaluation

Safety Parameters

- Vital signs: systolic (SBP) and diastolic (DBP) blood pressure, heart rate, and body temperature (tympanic).
- ECG (12-lead ECG)
- Safety laboratory tests: haematology, coagulation, plasma biochemistry.
- Presence of anti-LR12 antibodies
- Adverse events: from screening until study completion.

Pharmacokinetics

Plasma concentrations of LR12 will be measured by a validated LC-MS/MS assay and analysed using a non-compartmental analysis to obtain estimates of the PK parameters

Pharmacodynamics (exploratory)

sTREM-1, immune and vascular related biomarkers

Clinical Parameters (exploratory)

- Resolution of organ dysfunction (SOFA score total and individual domains)
- Vasopressor use
- Invasive mechanical ventilation
- Renal support
- Time until shock reversal defined as cessation of vasopressor support for 24 hours
- Mortality at day 28 and at day 90

Statistical Methods

Descriptive Statistics

Demographics, baseline characteristics, and disposition data will be summarised by treatment group (Placebo, Dose level 1, Dose level 2 and Dose level 3).

Safety, pharmacodynamic, pharmacokinetic and clinical data will be summarised by treatment group (Placebo, Dose level 1, Dose level 2 and Dose level 3), and over time.

Qualitative variables will be presented using the number of patients, the number of missing values, the frequency and the percentage per modality.

Quantitative variables will be reported using the number of patients, the number of missing values, the mean, the standard deviation, the median, the first and the third quartiles, the minimum and the maximum.

Geometric means and CV may be presented for variables with a skewed distribution.

Between groups comparisons are calculated using an independent t-test or ANOVA-test for quantitative variables with a parametric distribution, or Mann-Whitney-test or Kruskal Wallis-test for variables with a non-parametric distribution.

Cytokine distribution and vital signs over time are analysed by a repeated measures ANOVA (mixed models), if significant followed by the Bonferroni post-hoc test.
Data is tested for normality using Kolmogorov-Smirnov-test

HISTORY OF CHANGES

Changes from version 3.1 of the study protocol, dated 08 January 2018

- Introduction of retrospective data collection and exploratory post-hoc analysis of
  - Additional SOFA score data to replace data treated as missing in the original analysis
  - Duration of ICU stay
- Implementation of non-substantial change on plasma sample use documented on note to file dated 08 October 2018

Study protocol version 4.0 applies to study sites outside of France only

Changes from version 2.1 of the study protocol, dated 31 October 2017

- Addition of an interim analysis (section 15.4)
- Clarification of concomitant medication recording
- Minor corrections and clarifications

Study protocol version 3.0 dated 04 January 2017 applies to study sites outside of France only

Changes from version 1.3 of the study protocol, dated 12 September 2017

- Addition of blood samples for DNA analyses related to the TREM-1 signalling pathway
- Addition of a paragraph detailing the analysis and storage of blood samples
- Blood levels of sTLT-1 will not be analysed
- Name change of IMP management provider implemented
- Rating of Adverse Events updated for consistency with eCRF
- Minor corrections and clarifications

Study protocol version 2.0 dated 31 October 2017 applies to study sites outside of France only

Changes from version 1.2 of the study protocol, dated 29 August 2017

- Minor corrections and clarifications on the timing of blood samples in tables 1 and 2

These changes are **classified as non-substantial** by the sponsor according to the EU Clinical Trials Directive and section 8.2 of this study protocol.

Study protocol version 1.2, dated 29 August 2017 implemented the following changes from version 1.0 of the study protocol, dated 20 February 2017

- Changes requested by the French ANSM for sites in France:
  - Addition of exclusion criterion “APACHE II score <14”
  - Measurements of interferon-γ on days 1, 3, 5 and 28
  - Additional timepoint for the measurement of anti-drug antibodies on day 10
  - Direct antibody test (direct Coombs) at baseline (pre-dose), days 10 and 28
  - Addition of free bilirubin to the biochemistry laboratory parameters
  - Update of SUSAR reporting requirements for France
- Minor corrections and clarifications

Study protocol version 1.1 is only applicable to sites in the Netherlands

2 TABLE OF CONTENTS

List of Tables

List of Figures

3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

°C	Degree Celsius
ABG	Arterial blood gases
ADA	Anti-Drug Antibody
AE	Adverse event
ANOVA	Analysis of variance
APACHE	Acute Physiology And Chronic Health Evaluation
BMI	Body mass index
CCC	Clinical coordination centre
Cmax	Maximum concentration
CPR	Cardiopulmonary resuscitation
CRF	Case report form
CRO	Contract research organisation
d/D	Day
DBP	Diastolic blood pressure
dl	deciliter
DSMB	Data safety monitoring board
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EoI	End of Infusion
EoS	End of Study
GCP	Good clinical practice
h/H	hour
i.v.	intravenous
ICF	Informed consent form
ICH	International council for Harmonisation
ICU	Intensive care unit
IMP	Investigational medicinal product
kg	Kilogram
LC	Liquid chromatography
LR12	Active pharmaceutical ingredient in MOTREM
LPLV	Last patient last visit
MAP	Mean arterial pressure
mg	Milligram
mM	Millimolar
MOTREM	Clinical formulation of LR12
MS	Mass spectrometry
NOAEL	No Observed Adverse Effect Level
P/F	PaO_2/FiO_2 ratio of arterial oxygen partial pressure to fractional inspired oxygen
PD	Pharmacodynamics
Ph.Eur.	Pharmacopoea Europaea
PK	Pharmacokinetics
PW	Premature withdrawal
Q	Quarter (calendar)
QT	QT inverval (ECG)
QTc	Corrected QT interval
RNO	Ribonucleic acid
SAE	Serious Adverse Event
SBP	Systolic blood pressure

SNP	Single Nucleotide Polymorphism
SOFA	Sequential Organ Failure Assessment
SOM	Study operations manual
sTLT-1	Soluble TREM Like Transcript 1
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

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.

Sponsor's Officer Jean-Jacques GARAUD, MD, INOTREM	Date:	Signature:
Project Manager Valérie CUVIER, INOTREM	Date:	Signature:
Study Statistician Aude Lasfargues ASCOPHARM Groupe NOVASCO	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	Date:	Signature:

4.3 Investigator's Agreement

I have read this INOTREM SA Protocol No. MOT-C-201

Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of 3 Doses of MOTREM in Patients with Septic Shock.

A Randomised, Double-blind, Two-Stage, Placebo Controlled Study

I have fully discussed the objectives of this trial and the contents of this protocol with INOTREM SA representative.

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 authorisation from. It is, however, permissible to provide information to a patient in order to obtain consent.

I agree to conduct this trial according to this protocol and to comply with its requirements, patient to ethical and 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 INOTREM SA 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 INOTREM SA

Investigator (print name)	Date:	Signature:

5 STUDY PERSONNEL AND STUDY ADMINISTRATIVE STRUCTURE

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6 INTRODUCTION

6.1 Sepsis

For many years, the clinical features of sepsis were considered the result of an overly exuberant inflammatory host response. More recently, it has become apparent that infection triggers a much more complex, variable and prolonged host response (1,2). In general, proinflammatory reactions (directed at eliminating invading pathogens) are held responsible for "collateral" tissue damage in severe sepsis, whereas anti-inflammatory responses are implicated in the enhanced susceptibility to secondary infections. Key inflammatory reactions during sepsis include activation of leukocytes, the release of cytokines and chemokines, activation of the coagulation system and activation of endothelial cells (3). Inflammatory reactions are perpetuated in sepsis at least in part due to the release of so-called damage-associated patterns (or alarmins) from injured host cells (4). On the other hand, patients with sepsis demonstrate evidence of immune suppression, which is characterised (amongst other) by a reduced capacity of leukocytes to react to bacteria or bacterial products (5). Sepsis-induced immune suppression is characterised by loss of immune cells due to apoptosis, and held responsible for secondary nosocomial infections and late mortality (2,5).

An international group of experts has recently updated the criteria for the clinical diagnosis of sepsis and septic shock ("Sepsis-3") (6).

With an incidence of approximately 150 cases of hospital treated severe sepsis per 100,000 inhabitants in the "western" world (USA, Europe, Australia) and mortality rates of almost 30%, severe sepsis is a leading cause of death accounting for up to 5 million deaths worldwide (7). Epidemiological data in Europe confirm this information. The direct costs for the treatment were estimated to approx. EUR 30,000 per sepsis case, with costs higher in the US and lower in Europe. However, indirect costs from the loss of productivity were estimated to account for 70-80% of cost (8).

6.2 Treatment of Sepsis

The Surviving Sepsis Campaign was created in 2002 and covers severe sepsis management guidelines and a sepsis performance improvement program, composed by an international consortium of critical care, infectious disease, and emergency medicine professional societies. The second revision of the guidelines was published in 2013 (9). The most important components of the guidelines are structured in two "bundles" of care: an initial management bundle to be accomplished within 3-6 hours of presentation and a management bundle to be accomplished within 24 hours. Implementation of the bundles is associated with improved outcome (10).

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 pus drainage 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 sepsis. It is expected that sepsis 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 severe sepsis.

6.3 MOTREM 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 (11–14) 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") (15), which is responsible for the onset and progression of the disease.

LR12 is a 12 amino-acid peptidic fragment derived from TREM-Like Transcript-1 (TLT-1), a receptor protein belonging to the TREM-1 family. LR12 can bind to ("trap") TREM-1 ligand and thereby modulating the amplification of the immune response caused by the activation of TREM-1 both in sepsis and myocardial infarction (16,17).

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 LR12 *in vitro* in a dose dependent manner. In non-activated resting lymphocytes LR12 does not modify several intracellular signalling pathways analysed, including those involved in inflammation.

As sepsis is a life-threatening disease characterised by a hyperactivated immune response, it is of paramount importance to consider the safety of LR12, 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 LR12 was associated with protective effects especially on the intensity 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 LR12 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 LR12 also resulted in reduction of sepsis-induced tissue abnormalities and showed protective effects on the cardiovascular system. In addition, the administration of LR12 improved bacterial clearance in mouse model of peritonitis. In a mini-pig model of peritonitis, the administration of LR12 led to a significant decrease of vasopressor (norepinephrine) administration which translates to a substantial protective effect of the cardiovascular system. LR12 also prevented sepsis-induced tissue abnormalities and dysfunctions in this model.

During an experimental monkey endotoxemia model, the administration of LR12 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-α, CCL2, CCL3 and CCL4 were diminished to intermediate levels but not completely abrogated.

Animal toxicity studies showed that treatment with MOTREM (formulated LR12) was safe and well tolerated up to doses of 140 mg/kg/day.

In a phase I study in healthy volunteers, treatment with MOTREM was found to be safe and well tolerated up to the highest dose tested (6 mg/kg/h for 7h45).

For details please refer to the current Investigator's Brochure.

MOTREM, therefore, represents a new class of anti-sepsis drug. 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 sepsis.

The aim of this study in patients with septic shock is to obtain information on the safety, tolerability, pharmacokinetics and preliminary pharmacodynamics and efficacy of MOTREM. Data from this study will help to design subsequent studies in patient populations clinically and therapeutically relevant with this new class of compound.

6.4 Risk-Benefit Evaluation

6.4.1 Potential Benefits

MOTREM (LR12) will be given to patients mainly for research and development purposes. Although a beneficial effect of MOTREM has not yet been confirmed in humans, patients receiving IMP may benefit from its pharmacological action.

Over the long-term, the larger patient population with septic shock may benefit from MOTREM if its development will be successful.

6.4.2 Potential Risks

MOTREM was found to be safe and well tolerated during preclinical safety pharmacology and toxicology testing (NOAEL was defined as 140 mg/kg/day for 14 days). In addition, MOTREM was found to be safe and well tolerated up to the highest dose tested (6 mg/kg/h for 7h45) in a phase I clinical study in healthy volunteers. There was no evidence of immunogenicity of MOTREM nor the appearance of anti-MOTREM antibodies (ADA).

There is currently no clinical experience with MOTREM in patients with septic shock.

As with all protein products, administration of MOTREM may result in immunogenicity. Immunogenicity-related risks include lack of efficacy, hyper-acute or acute reactions, delayed reactions or autoimmunity. LR12 is a peptide derived from a highly conserved human protein; it is expected to have a low immunogenic profile. An exposure to study drug of up to five days is not expected to result in triggering an immune response in the study patients. However, since the possibility of triggering an immune response against it in humans still exists, ADA responses will be monitored and patients will be surveyed for other manifestation of immunogenicity-related reactions.

Because of its mechanism of action, MOTREM may have an impact on the immune system, either on immune cells or on immune responses. Since MOTREM targets activated immune cells in septic shock patients, the treatment with formulated LR12 may interfere with inflammatory/immune responses in an undesired way. However, in preclinical models, treatment with LR12 resulted in a diminution of proinflammatory cytokine expression and concentration and not in a complete abrogation of cytokine responses. In addition, LR12 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 MOTREM, which describes potential risks of MOTREM 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 favourable because (i) throughout the study, all patients receive standard therapy for the treatment of their septic shock, (ii) progression to next dose level/next stage only after evaluation of data from previous groups/cohorts and approval from an independent Data Safety Monitoring Board (DSMB) and (iii) patients with a deterioration of their disease will be withdrawn from the study.

7 STUDY OBJECTIVES

Primary

- To evaluate the safety and tolerability of MOTREM in patients with septic shock

Secondary

- To evaluate the effects of MOTREM exposure over up to 5 days in patients with septic shock
- To evaluate the PK/PD and dose/PD relationships to TREM-1 pathway related markers
- To evaluate the effect of MOTREM on transcriptomics
- To evaluate the effect of MOTREM on clinical parameters (e.g. vasopressor doses, vasopressor-free days, ventilator-free days, mortality)

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan Description

This is a randomised, double-blind, two-stage, placebo controlled study. It consists of 2 stages with a similar treatment regimen, in which 0.3, 1.0 or 3.0 mg/kg/h of MOTREM is tested versus placebo.

All patients with a diagnosis of septic shock will be considered for study participation. The applicable local regulations and requirements for informed consent will be followed. All potential study patients will undergo standard care management procedures.

After screening for eligibility, patients will be randomised to one of the treatment arms. They will then either receive a 5 mg/kg loading dose of MOTREM over 15 minutes followed by a continuous i.v. infusion of MOTREM or a matching placebo on top of standard of care.

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 the determination of LR12 plasma concentrations and exploratory pharmacodynamic analyses will be collected before and throughout the treatment period.

Patients will be treated until 12 (±2) hours after the resolution of their septic shock (defined as vasopressor withdrawal) with a maximum treatment duration of 5 days (120 (±2) hours).

The status of patients after 28 and 90 days will be collected.

Stage 1 is investigating multiple ascending doses of MOTREM or placebo in a sequential design in cohorts of 4 patients (3:1 randomisation). After completion of a cohort (for up to 5 days of infusion), safety and PK data (limited to PK data available) will be reviewed by an independent DSMB and the study will progress to the next cohort/stage.

A flowchart of the sequential dose levels in stage 1 is provided in Figure 1.

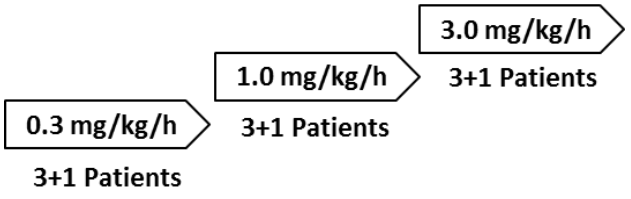

Figure 1: Flow Chart of sequential Dose Levels tested in Stage 1

A flowchart for stage 1 (per cohort) is provided in Figure 2.

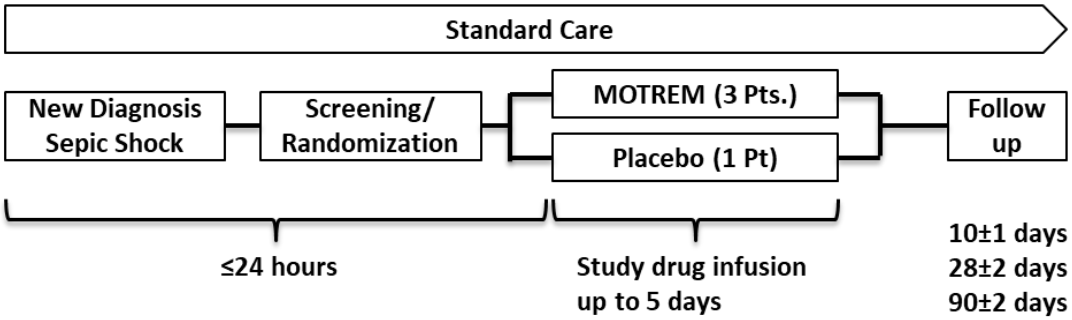

Figure 2: Flow Chart Stage 1 (per cohort)

Stage 2 investigates 3 doses of MOTREM in a randomised parallel-group design. The treatment regimen for the patients is identical to stage 1. A flowchart for stage 1 is provided in Figure 3.

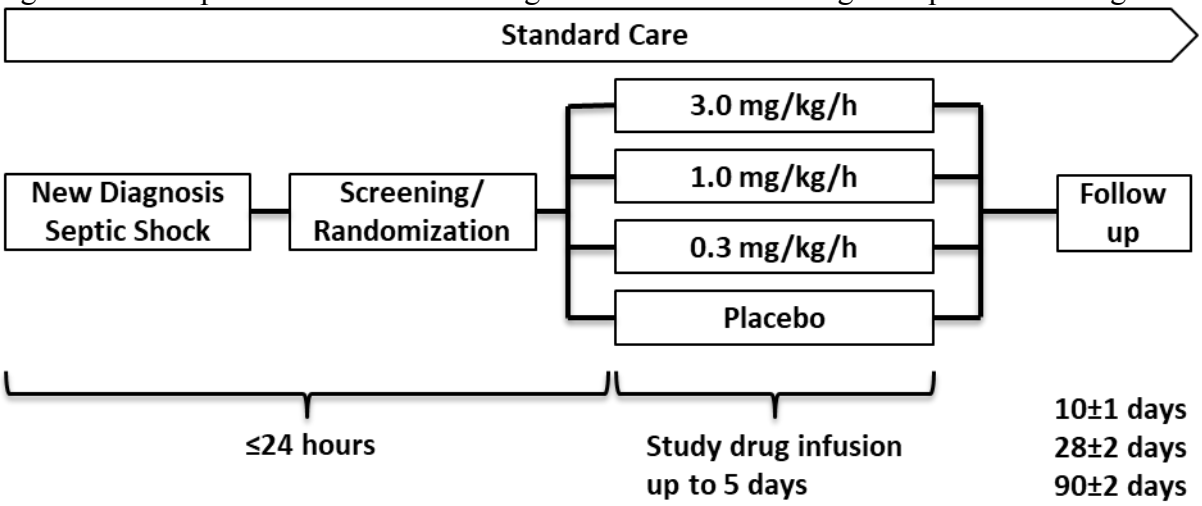

Figure 3: Flow Chart Stage 2

All assessments performed in the study are summarised in the study schedule provided in Table 1 and Table 2.

Table 1: Study Schedule

	Screen.	**Treatment**						**Day 10**	**EoS**	**Follow-up**
	≤24H	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5/ EOI**	**10±1d**	**28±2d**	**90±2d**
Assessment										
Informed consent	X									
Inclusion/exclusion criteria	X									
Medical history and demographics	X									
Previous therapies[1]	X									
APACHE II Score	X									
Pregnancy test (female patients)	X									
Height	X									
Weight	X						X		X	
Vital Signs	X	X[2]	X	X	X	X	X		X	
ECG	X	X[2]	X	X	X	X	X		X	
SOFA Score/organ dysfunction	X	X[2]	X	X	X	X	X		X	
Call to the CCC	X									
Randomisation	X									
Study Drug Infusion		X	X	X	X	X	X			
Concomitant Therapies		X	X	X	X	X	X		X	
Vasopressor		X	X	X	X	X	X		X	
Invasive mechanical ventilation		X	X	X	X	X	X		X	
Intubation		X	X	X	X	X	X		X	
Mortality			X	X	X	X	X		X	X
Adverse Events		X	X	X	X	X	X		X	X[5]
Arterial blood gases, P/F ratio	X	X[2]	X	X	X	X	X		X	
Clinical Laboratory (see table 2)	X	X[2]	X	X	X	X	X		X	
Anti-drug antibodies (ADA, see table 2)		X[2]						X	X	
Direct antibody test (see table 2)		X[2]						X	X	
PK samples (see table 2)		X[2]	X	X	X	X	X[4]			
Biomarker samples (see table 2)		X[2]	X	X	X	X	X		X	
RNA profiles (see table 2)		X[3]	X		X		X		X	
Plasma sample for retention (see table 2)		X[2]	X							
Blood sample for pharmacogenetics		X								
EoI: end of infusion; EoS: end of study										

1: All medication taken within the last 24 hours before start of treatment should be documented
2: Before initiation of treatment
3: Sampling time points at D0 are detailed in Table 2
4: Sampling time points at EOI are detailed in Table 2
5: Mortality status and relevant changes to patient's condition will be collected

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

Test	Parameters	Timepoints
Chemistry[1]	Aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total and free bilirubin, creatinine, urea, glucose, sodium, potassium, chloride, calcium, inorganic phosphate, total protein, CRP, albumin, lactate	daily, from routine laboratory assessments, first routine sample of the day
Haematology[1]	Haemoglobin, haematocrit, leucocytes, basophils, eosinophils, neutrophils, lymphocytes, monocytes, platelet count	daily, from routine laboratory assessments, first routine sample of the day
Coagulation[1]	International Normalized Ratio (INR)	daily, from routine laboratory assessments, first routine sample of the day
Direct antibody test[1]	Direct Coombs test	Baseline (pre-dose), D10 and FU day 28
Anti-drug antibodies[2]	Anti-drug antibodies	Baseline (pre-dose), D10 and FU day 28
MOTREM PK[2]	MOTREM circulating levels	Baseline (pre-dose), D1 to D5: daily. EOI PK (if feasible) 15 minutes before EOI and 10 min, 30min and 2h after EOI
Cytokines[2]	TNFα, IL-6, IL-8, IL-10, CCL2 (MCP-1), IFNγ	Baseline (pre-dose), D1, D3 and D5, FU day 28
Activation of vascular endothelium[2]	soluble CD62E (E selectin), VEGFR-1, VCAM-1, Ang-1, Ang-2	Baseline (pre-dose), D1, D3 and D5, FU day 28
sTREM-1[2]	soluble TREM-1	Baseline (pre-dose), D1 to D5: daily, FU day 28
RNA profiles[2]	whole leukocyte RNA profiles (by arrays)	Baseline (pre-dose), 1h, 6h, 12h D1, D3 and D5, FU day 28
Plasma sample for retention	A plasma sample for future exploratory analyses will be stored (see section 12.12.3)	Baseline (pre-dose), D1
Blood sample for pharmacogenetic analyses[2,3]	Single Nucleotide Polymorphisms of TREM-1 pathway-related genes.	Baseline, other timepoints are acceptable

EOI: End of infusion of study drug
1: Site; 2: Centralised; third party laboratory provider; 3: optional with separate informed consent

8.2 Adaptive Design

This study incorporates the use of an adaptive design. Study specific adaptive features and their limits are described in Table 3.

Table 3: Adaptive Protocol Features.

Adaptive study design areas	Features	Limits
Repetition of cohorts	• Cohorts in stage 1 can be repeated in order to obtain more safety and PK data	• Each cohort in stage 1 can be repeated only once • The randomisation will follow the originally planned system
Dose levels	• Dose levels in stage 2 of the study can be dropped or adjusted in accordance with PK, safety and tolerability data collected up to the decision-making point	• The maximum dose will not exceed 5.0 mg/kg for the loading dose and 3.0 mg/kg/h for the maintenance dose • If a dose level is dropped, the planned number of patients may be reassigned to the remaining dose levels.
Samples and assessments	• Timing of PK and/or biomarker samples may be adjusted in accordance with evolving data and dosing schedule. • Additional or less PK and/or biomarker samples may be taken in accordance with evolving data and dosing schedule. • Biomarker measurements may be added or removed in accordance with evolving data and dosing schedule (e.g. mTREM-1)	• Minimum: sufficient PK samples according to the respective study objective • Study specific maximum blood volume will not be exceeded (see section 12.12.8).
Time Window between onset of shock and initiation of treatment	• The time window of 24 hours between onset of shock and start of study drug infusion may be shortened for stage 2 in accordance with evolving feasibility data from stage 1	• The allowed time window in stage 2 will not be shorter than 12 hours

8.3 Study Duration and End-Study Definition

The duration of this study for each patient will be a maximum of 13 weeks (including screening, up to 5 days of treatment and follow-up assessments 28 and 90 days after randomisation). The patient recruitment is planned to last for 9-12 months, starting in the second quarter of 2017. The actual overall study duration or patient recruitment may vary.

The end of study is defined as the last patient, last visit (LPLV).

8.4 Rules for Dose Escalation/Progression to Stage 2

An independent DSMB will review and assess blinded serious adverse events (SAEs), adverse events and, PK data (limited to PK data available) after the completion of each dose level. No formal statistical analysis will be performed. The DSMB will assess if the reported AEs have a causal relationship with the IMP and if the benefit-risk assessment is still favourable and make a decision for progression to the next dose level (e.g. from cohort 1 to 2 or from cohort 3 to

stage 2), termination or modification of the study based on the effects of the interventions under study.

There is an option to have ad-hoc DSMB meetings to discuss urgent issues should the need arise.

8.4.1 Data Safety Monitoring Board (DSMB)

An independent data safety monitoring board (DSMB) will monitor the safety of the study. The DSMB will comprise experts with experience in the treatment of sepsis and septic shock and the conduct of clinical trials in this indication. The DSMB will be responsible for:

- Examining blinded accumulated safety and PK data, with no formal statistical analysis performed, in order to make recommendations for the progression of the study to next dose (stage 1) or progression from stage1 to stage 2.
- Reviewing serious adverse events (SAEs) and toxicity data
- Reviewing the general progress of the clinical study with regard to accrual/withdrawals or drop-out rates and clinical study conduct.

Where necessary, DSMB members may have access to unblinded safety data for one or more patients; however, no members of the study team (at INOTREM, at the Contract Research Organisation [CRO] or the sites) will have access to unblinded data until after database lock is declared. In case unblinded data needs to be handled or analysed before database lock, these tasks will be performed by persons independent from the study team.

The DSMB will provide recommendations for stopping or continuing the study based on safety results. The roles, responsibilities, and operating procedures of the DSMB will be formally defined in a DSMB charter which will be developed in consultation with DSMB members.

8.4.2 Data Requirements

After each cohort, the DSMB will assess the minimum safety, tolerability and PK data required prior to dose escalation/progression. Prior to each DSMB meeting, an interim safety report will be prepared for that cohort presenting the relevant safety and tolerability data.

The following data will be required: (i) all SAE data (ii) available AE data and (iii) available PK data.

8.5 Rationale for Study, Doses and Control Groups

8.5.1 Rationale for Conducting Study

The rationale for taking MOTREM into further development is the expectation that this compound could be an effective new anti-sepsis therapeutic agent. This study represents the first time that MOTREM will be administered to patients with septic shock. Data from this study will help to design subsequent therapeutic studies with this new class of compounds.

Consequently, this study intends to confirm the safety, tolerability and PK obtained in the healthy volunteer study. In addition, it will explore the pharmacodynamic effects of MOTREM.

8.5.2 Rationale and Justification for Placebo Control

During this study, all patients will be treated with standard therapy. On top of this therapy, MOTREM or placebo will be added. No medications will be withdrawn for the purpose of this study. Placebo was chosen as a comparator in order to investigate the safety and pharmacodynamics of MOTREM in this study population.

8.5.3 Rationale for Dose Levels

There will be a loading dose of 5 mg/kg administered within 15 minutes in all dose groups. The maintenance dose levels planned for this study (0.3, 1.0 and 3.0 mg/kg) do represent the expected therapeutic window as determined from in vitro and animal studies. Fifteen-minutes loading doses of 0.5 to 5mg/kg and maintenance doses ranging from 0.03 mg/kg/h to 6 mg/kg/h were found to be safe and well tolerated in the completed phase I study (MOT-C-104) in healthy volunteers. In addition, this dose range is fully covered by preclinical animal toxicity and safety pharmacology studies. In preclinical studies, MOTREM has been safely administered to cynomolgous monkeys during 14 days at a dose of 5.8 mg/kg/h and for a total cumulated dose of 140 mg/kg/day and 1960 mg/kg during the whole period.

In this study, patients will start receiving 0.3 mg/kg/h for a maximum of 5 days (7.2 mg/kg/day and 36 mg/kg for the whole period) and, if safe, dose will be escalated to a maximum of 3 mg/kg/h for up to 5 days (72 mg/kg/day and 360 mg/kg for the whole period).

8.5.4 Rationale for Exposure Time

The rationale for administering MOTREM up to 5 days is that immune initial inflammatory loop is activated during this period (15). Indeed sTREM-1 circulating levels are very high during these first days, in particular in patients with high mortality, and is probably a sign of TREM-1 pathway activation and thus an exacerbation of inflammatory responses (18). Stage 1 of the study consists of an ascending dose design and escalation to the next dose level will occur after review of accumulated safety data by the DSMB.

9 SELECTION OF PATIENTS

9.1 Number and Source of Patients

A total of 48 patients is planned. There will be 12 patients in stage 1 (4 per dose level) and 36 patients in stage 2 (9 per dose level). No formal sample size calculation was performed. The number of patients was chosen on the basis of similar studies investigating the safety, tolerability and pharmacokinetics of a drug product. In stage 1, the patients will be treated in three sequential cohorts with ascending dose levels of 4 patients each. Stage 2 of the study has a parallel-group design, where three dose levels of MOTREM will be compared to placebo.

Patients admitted to the participating intensive care units (ICUs) for septic shock will be screened at admission for eligibility. The eligibility criteria are identical between the two stages of the study.

The maximum number of patients according to the adaptive features of the study protocol will not exceed 66 patients, as specified below:

- Each cohort in stage 1 can be repeated once for the collection of additional safety data
- In each cohort in stage 1, one patient not completing 24 hours of study drug infusion will be replaced

At sites, who are conducting more than one clinical trial competing for the same patient population, a selection bias should be avoided. Random allocation of patients with the diagnosis to the different trials is an acceptable method for the minimisation of such bias and is recommended (19). A respective procedure should be in place at these sites.

9.2 Inclusion Criteria

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

1. Provide written informed consent (proxy/legal representative/independent physician/emergency consent) according to local regulations
2. Age 18 to 80 years

Sepsis

3. Documented or suspected infection: lung, abdominal or elderly UTI (≥65 years)
4. Organ dysfunction defined as acute change in SOFA score ≥ 2 points

Shock

5. Refractory hypotension requiring vasopressors to maintain MAP ≥65mm Hg despite adequate volume resuscitation of at least 20 ml/kg within 6 hours (according to Surviving Sepsis guidelines, see Appendix 1)
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 will exclude a patient from study enrolment:

1. Previous episode of septic shock (vasopressor administration) within current hospital stay
2. Underlying concurrent immunodepression (specified in appendix 2)
3. Solid organ transplant requiring immunosuppressive therapy
4. Known pregnancy (positive serum pregnancy test)
5. Prolonged QT syndrome (QTc ≥ 440 ms)
6. Shock of any other cause, e.g. hypotension related to gastrointestinal bleeding
7. Ongoing documented or suspected endocarditis, history of prosthetic heart valves
8. End-stage neurological disease
9. End-stage cirrhosis (Child Pugh Class C)
10. Acute Physiology And Chronic Health Evaluation (APACHE) II score ≥ 34
11. End stage chronic renal disease requiring chronic dialysis
12. Home oxygen therapy on a regular basis for > 6 h/day
13. Severe obesity (BMI ≥ 40)
14. Recent CPR (within current hospital stay)
15. Moribund patients
16. Decision to limit full care taken before obtaining informed consent
17. Participation in another interventional study in the 3 months prior to randomisation
18. APACHE II score <14

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 centre (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 under the following phone number:

+32 (2) 764 27 80

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
- Use of/need for a prohibited medication which in the opinion of the Sponsor or Investigator may jeopardise the study results or represent a risk to the participant
- Major violation of the protocol
- Is withdrawn from the study upon the request of Sponsor, including if Sponsor terminates the study.

As far as possible, all examinations scheduled for the final study day (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" as well as survival status at days 28 and 90 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 on page 42.

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.

9.5.1 Replacement of Patients

In stage 1 of the study, patients not completing 24 hours of study drug infusion will be replaced. For replaced patients, the same randomisation scheme will be utilised to ensure distribution of patients to dose levels as planned. No more than one patient per cohort will be replaced.

In stage 2 of the study, patients will not be replaced.

9.5.2 Withdrawal of Blood and Urine Samples

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

9.6 Patients of Reproductive Potential

Since MOTREM 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 CTFG guidance (20) will be applied. All female patients will have a serum pregnancy test performed before enrolment into the study. Since the patients will be hospitalised in an ICU during treatment with IMP, contraceptive measures and additional pregnancy tests are not considered required. Since the half-life of MOTREM 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)

MOTREM is prepared as a stable lyophilised product in L50 type I glass vials containing 400 mg of free base lyophilised LR12 peptide in sodium citrate and arginine buffer at pH 5.5. The powder is to be solubilised with 40 mL of saline solution for injection to yield a clear and colourless solution of MOTREM at 10 mg/mL. Table 4 shows the composition of MOTREM in vials and 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 MOTREM Drug Product and as Reconstituted Solution

Product	***Function***	**Drug Product (per Vial)**		**Reconstituted Solution[1]**
LR12	*API*	400 mg		10 mg/mL (7.5 mM)
Trisodium citrate	*Buffer*	103 mg		2.6 mg/mL (10 mM)
Arginine	*Solubilisation and lyophilisation bulking agent*	139 mg		3.5 mg/mL (20 mM)
HCl	*pH adjustment*	q.s. pH 5.5		-
	Diluent	Diluent: water for injection.		Diluent for reconstitution: NaCl 9 mg/mL (0.9%)
1: after reconstitution with 40 mL of 0.9% Sodium Chloride for Injection Ph Eur				

10.2 Placebo

The placebo used in this study will be a saline solution (i.e. NaCl 0.9%). Since placebo and IMP have both a clear appearance as formulated LR12 is diluted in saline solution, this assures blinding of the study treatment. The saline solution will be either provided by the site or by the sponsor.

10.3 Doses and Treatment Regimen

Single doses of MOTREM (LR12) or matching placebo are planned to be administered i.v. as detailed in Table 5 and Table 6.

Table 5: Dosing of IMP (MOTREM or Matching Placebo) in Stage 1

Dose Group	**i.v. loading dose T = 15'**	**Maintenance i.v. dose T = up to 5 days**	**Number of Patients**	
	[mg/kg]	**[mg/kg/h]**	**Active**	**Placebo**
Cohort 1	5.0	0.3	3	1
Cohort 2	5.0	1.0	3	1
Cohort 3	5.0	3.0	3	1

Table 6: Dosing of IMP (MOTREM or Matching Placebo) in Stage 2

Dose Group	i.v. loading dose T = 15'	Maintenance i.v. dose T = up to 5 days	Number of Patients
	[mg/kg]	[mg/kg/h]	
Dose Level 1	5.0	0.3	9
Dose Level 2	5.0	1.0	9
Dose Level 3	5.0	3.0	9
Placebo	0	0	9

MOTREM or matching placebo will be administered by the investigator or delegate and the details of dosing will be recorded in the CRF.

The study drugs will be dispensed by the pharmacy staff at the clinical study site. The pharmacy staff or a dedicated unblinded person independent from the study team will be responsible for assembly and labelling of dosing containers according to randomisation schedules and assigned dose level. The amount/ volume of study drug to be administered will be determined based on the assigned dose level for a particular cohort. The procedure for preparing the study drugs and the volume to be prepared for each individual patient dose will be detailed in a Pharmacy Worksheet.

Detailed instructions for dose administration is included in the Study Operations Manual (SOM).

10.4 Labelling of Study Drug

The labelling of the study drugs will be in compliance with Good Manufacturing Practice (GMP) specifications, as described in The Rules Governing Medicinal Products in the European Union, Volume 4, Annex 13, Investigational Medicinal Products, and any other or local applicable regulations.

Sample label(s) will be submitted to the competent regulatory authorities according to the submission requirements.

10.5 Drug Accountability

The designated pharmacy staff at the clinical study site will maintain accurate records of receipt and the condition of all study drugs, including dates of receipt. In addition, accurate records will be kept by the pharmacy staff of when and how much study drug is dispensed and used by each patient in the study. Any reason for deviation from the protocol dispensing regimen must also be recorded.

Drug accountability records and inventory will be available for verification by the Sponsor or designee. At the completion of the study, there will be a final reconciliation of all study drugs.

Study drug must not be used for any purpose other than the present study. Remaining study drug will be returned to the Sponsor or its agent or destroyed at the clinical study site according to applicable regulations and only after receipt of written authorisation from the Sponsor.

10.6 Blinding and Procedures for Unblinding the Study

10.6.1 Methods for Ensuring Blinding

The study will be conducted in a double-blind fashion, whereby patients and clinical study site staff are blinded to study drug assignment.

The pharmacy staff or any other dedicated person preparing the investigational products will not be blinded to study drug assignment and will be responsible for the blinding of the study drug. During the study, the randomisation codes will be kept in the site's clinical trials pharmacy, accessible to the pharmacy personnel or any other dedicated person only. Upon completion of the study, after the database lock and after the blind is revealed, the randomisation list will be filed in the Study Master File.

10.6.2 Methods for Unblinding a Patient

Individual randomisation code for each randomised patient will be available from electronic Case Report Form (eCRF). The investigator may request unblinding of a patient's treatment assignment mainly in the case of an emergency, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the patient.

In the event of an emergency, an unblinding tool will be accessible from patient overview in the eCRF and allow to know for each patient his study drug assignment.

Unblinding should only be considered for the safety of the patient. If unblinding is deemed necessary by the investigator, the investigator or designee can unblind the patient's treatment allocation using a specific function in eCRF. The investigator or designee must note the date, time and reason for unblinding and inform the sponsor of unblinding as soon as practicably possible.

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

10.7 Prior and Concomitant Medications/Procedures

Medication taken by the patients on entry to the study or at any time during the study in addition to the investigational product, are regarded as concomitant treatments and must be documented in the appropriate sections of the eCRF.

Parenteral nutrition, vitamin supplements and stool softener will not be recorded in the eCRF.

Relevant previous treatments taken within 24 hours before start of treatment must also be documented in the CRF.

Concomitant medications will be recorded in the eCRF until 3 days after end of infusion (EOI).

Concomitant medications related to AEs (corrective drug required) should be recorded until D28.

Before enrolment into the study, all patients should receive standard of care, including fluid therapy, as recommended in the current version of the guidelines issued by the Surviving Sepsis Campaign (9).

10.7.1 Allowed and Not-Allowed Medications and Procedures

All treatments and procedures required for the treatment of the patient's illness are permitted.

The following concomitant treatments are not permitted during the treatment phase of this study (i.e. study drug infusion):

- Bolus glucocorticoid treatment exceeding 300mg of hydrocortisone or equivalent per day for a maximum of three days

11 STUDY PROCEDURES AND SCHEDULE

An overview on study procedures and schedule is provided in the flowcharts in Figure 1, Figure 2, Figure 3 on pages 21 and 22 and in Table 1 on page 23.

11.1 Obtaining Informed Consent

During screening for eligibility, before any study specific procedure was 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 enrolment in the study based on the inclusion and exclusion criteria and to obtain written informed consent.

Patients who meet all of the inclusion criteria and none of the exclusion criteria and have provided informed consent can be enrolled in the study.

Note: Before confirming the eligibility of a patient, adequate fluid therapy as recommended in the current guidance of the Surviving Sepsis Campaign (see appendix 1) should be applied.

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 invasive mechanical ventilation
- Time and details of fluid and vasopressor therapy
- Previous therapies (within 24 hours prior to screening)
- APACHE II score
- Serum pregnancy test in all female patients
- Physical examination
- Weight and height
- Vital signs
- ECG
- SOFA score
- Blood sample for arterial blood gases (ABG). P/F will be calculated, using equivalence tables for non-ventilated patients
- Clinical laboratory (see Table 2)
- Phone call with the CCC to approve patient inclusion in the study
- Randomisation

11.3 Treatment Period (Days 0 to Day 5)

After meeting all eligibility criteria (confirmed by the CCC, see section 1), eligible patients will be randomised and treatment with MOTREM i.v. will be initiated according to the schedule provided in Table 5 or Table 6.

Note: Treatment with MOTREM 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 before the first administration of study drug:

- Confirmation of patient's eligibility (inclusion exclusion criteria)

- Confirmation of septic shock and time window for treatment initiation (≤24 hours after onset)
- Concomitant therapy
- SOFA score
- Vital signs
- ECG
- Vasopressor use
- Invasive mechanical ventilation
- Intubation
- Adverse events
- Blood sample for ABG and P/F
- Blood samples for laboratory tests (according to schedule provided in Table 2):
  - Clinical Laboratory
  - Anti-drug antibodies (ADA)
  - Pharmacokinetics
  - Biomarkers
  - RNA profile
  - Plasma samples for retention
  - Pharmacogenetics (other timepoints are acceptable)
- Initiation of study drug i.v. treatment (according to Table 5 or Table 6)
- Direct antibody test (direct Coombs) before initiation of treatment with study drug

11.3.2 Treatment Period (Day 1 to Day 4)

During the treatment period of up to 5 days, the following assessments will be performed daily (approximately at the same time of day):

- Concomitant therapy
- SOFA score
- Vital signs
- ECG
- Vasopressor use
- Invasive mechanical ventilation
- Intubation
- Mortality
- Adverse events
- Blood sample for ABG and P/F
- Blood samples for laboratory tests (according to schedule provided in Table 2):
  - Clinical Laboratory
  - Pharmacokinetics
  - Biomarkers
  - RNA profile
  - Plasma samples for retention (Day 1 only)
- Continued treatment with MOTREM i.v. (according to Table 5 or Table 6)

11.3.3 End of Infusion/Day 5

Patients will be treated until 12 (±2) hours after the resolution of their septic shock (defined as vasopressor withdrawal) with a maximum treatment of 5 days (120 (±2) hours). An

interruption of vasopressor treatment of up to 6 hours is permitted and not considered vasopressor withdrawal).

Patients may also be withdrawn from treatment for other reasons (see section 9.5).

At the end of treatment, the i.v. infusion will be stopped and the following assessments will be performed:

- Concomitant therapy
- SOFA score
- Vital signs
- Weight
- ECG
- Vasopressor use
- Invasive mechanical ventilation
- Intubation
- Mortality
- Adverse events
- Blood sample for ABG and P/F
- Blood samples for laboratory tests (according to schedule provided in Table 2):
  - Clinical Laboratory
  - pharmacokinetics
  - biomarkers
  - RNA profile

If the treatment is stopped any day before D5, the assessments listed above will be performed only once the day of the end of infusion.

For all patients alive, the SOFA score will however be calculated until day 5, no matter when the study treatment stopped. This data will be collected to the extent available in source data and analysed post-hoc (see section 15.5).

11.3.4 End of Study / Premature withdrawal

An End of Study visit will be performed at 28±2 days after the initiation of MOTREM treatment.

The following assessments will be performed:

- Concomitant therapy
- Weight
- SOFA score
- Vital signs
- ECG
- Vasopressor use
- Invasive mechanical ventilation
- Intubation
- Adverse events
- Blood sample for ABG and P/F
- Mortality
- Serious adverse events
- Blood samples for laboratory tests (according to schedule provided in Table 2)
  - Clinical Laboratory

  - Anti-drug antibodies (ADA)
  - Biomarkers
  - RNA profile
- Direct antibody test (direct Coombs)

In case the patient was discharged already, effort should be made to perform as many assessments as reasonably possible. The reasons for missing values must be documented.

11.3.5 Follow-up Period

A follow-up visit will be performed at 90±2 days after the initiation of MOTREM treatment. A documented phone call to patient or carer is acceptable for this purpose.

The following assessments will be performed:

- Mortality
- Relevant changes to patient's condition

11.3.6 Additional Follow-up at Day10

The following assessments will be performed:

- Blood samples for laboratory tests (according to schedule provided in Table 2)
  - Anti-drug antibodies (ADA)
  - Direct antibody test (direct Coombs)

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 on entry to the study or at any time during the study in addition to the investigational product, are regarded as concomitant treatments and must be documented on the appropriate pages of the eCRF.

Concomitant medications will be recorded in the eCRF until 3 days after end of infusion (EOI).

Concomitant medications related to AEs (corrective drug required) should be recorded until D28.

Relevant previous treatments taken within 24 hours before the study must also be documented in the eCRF.

12.3 APACHE II Score

The Acute Physiology and Chronic Health Evaluation II score is a severity-of-disease classification system (21). It is generally applied within 24 hours of admission of a patient to an intensive care unit (ICU). An integer score from 0 to 71 is computed based on measurements of:

- $AaDO_2$ or PaO_2 (depending on FiO_2)
- Temperature (rectal)

- Mean arterial pressure
- pH arterial
- Heart rate
- Respiratory rate
- Sodium (serum)
- Potassium (serum)
- Creatinine
- Haematocrit
- 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 of ≥ 34 or <14.

12.4 Vital Signs

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

12.5 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 each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems (22).

It will be calculated daily between screening and day 5 and at day 28 according to the following:

Respiratory System

PaO_2/FiO_2 (mmHg)	SOFA Score
< 400	1
< 300	2
< 200 and mechanically ventilated	3
< 100 and mechanically ventilated	4

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×10^3/ml	SOFA Score
< 150	1
< 100	2
< 50	3
< 20	4

Kidneys

Creatinine (mg/dl) [µmol/L] (or urine output)	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] (or < 200 ml/d)	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.

12.6 Electrocardiographic (ECG) Measurements

12-lead ECGs will be recorded daily at the time-points described in the study plan in Table 1 on page 23. Copies of the ECG printouts will be collected by the sponsor.

12.7 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 will be measured in centimetres and weight in kilograms. Where possible, measurements should be taken with patients wearing light clothing and without shoes using calibrated scales for all measurements. BMI will be calculated from the height and weight.

12.8 Requirement of Vasopressor, Mechanical Ventilation and Intubation

The beginning and end of study of vasopressor therapy, invasive mechanical ventilation and intubation will be documented in the eCRF.

12.9 Sepsis Related Clinical Events

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

- Death related to severe sepsis, that is, related to severe sepsis or a sequela of sepsis based on the interpretation of the investigator.
- Cardiovascular events: the need for vasoactive drugs, hypotension.
- Respiratory events: decreased PaO_2/FiO_2, 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 LFTs.
- 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.
- Systemic inflammatory response syndrome related criteria: tachypnea, hypopnea, leukocytosis, leukopenia, hypothermia, hyperthermia, tachycardia, or bradycardia.

12.10 Mortality Assessment

If a patient dies during the course of the study (time of informed consent to day 90 follow-up), the date and time of death will be documented. If possible, the cause of death will be documented.

12.11 Study Drug Infusion

The beginning and end of study of each drug infusion will be documented in the eCRF.

12.12 Duration of ICU Stay

The date and time of ICU discharge will be collected. This data will be collected to the extent available in source data and analysed post-hoc (see section 15.5).

12.13 Laboratory Tests

12.13.1 Local Laboratory Tests

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

Haematology, Chemistry and Coagulation

Assessments of haematology, chemistry and coagulation will be performed according to Table 2 on page 25.

Pregnancy Test (Female Patients)

A serum beta-HCG pregnancy test will be performed on all women of childbearing potential prior to inclusion into the study.

Direct Antibody Test (Direct Coombs) – Sites in France only

A direct antibody test (direct Coombs test) will be performed at the time points specified in Table 2 on page 25.

Arterial Blood Gases

Partial pressure of arterial oxygen (PaO_2) and carbon dioxide ($PaCO_2$) and pH will be documented at the time points specified in Table 2 on page 25.

12.13.2 Centralised Laboratory Tests

All centralised laboratory tests and procedures are described in detail in a separate manual.

Biomarkers and RNA Profiles

Blood samples for the assessment of biomarkers and RNA profiles will be collected throughout the study according to Table 2 on page 25. Details for sampling requirements, storage and shipment to the respective laboratories are described in the SOM.

Pharmacokinetic Assessments

For timing of individual samples refer to the Study Plan (Table 1and Table 2). The date and time of collection will be recorded on the appropriate eCRF.

PK Blood Samples: Venous blood samples for the determination of concentrations of LR12 (active ingredient of MOTREM) in plasma will be taken at the times presented in the Study Schedule (Table 1 and Table 2).

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 interference with the analyte.

Immunogenicity

The presence of anti-drug antibodies (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 analysis will be described in the laboratory manual.

12.13.3 Plasma Sample for Retention

A plasma sample for future exploratory analyses of biomarkers as described in Table 1 and 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 MOTREM 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 specimen will be subject to the confidentiality standards described in section 17.5.

12.13.4 Blood Sample for Pharmacogenetic Analysis

Certain polymorphisms in the gene coding for the TREM-1 and related genes could have an effect on the safety and efficacy of MOTREM. Therefore, one small blood sample for the future

exploratory analysis of these polymorphisms will be collected as described in Table 1 and Table 2. The total volume of blood sampling will remain unchanged as specified in section 12.12.5 below.

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 specimens will be subject to the confidentiality standards described in section 17.5.

The participation in this part of the study is voluntary and covered by a separate ICF.

12.13.5 Volume of Blood Sampling

Total blood volume sampled during the study in addition to standard care for each patient will be approximately 160 mL.

The total volume of blood that will be drawn from each patient in this study will be further specified in study operations manual. The actual amount withdrawn may be different per patient in case samples need to be repeated for technical reasons but will not exceed 250 mL.

12.13.6 Analysis and Storage of Blood Samples

All blood samples will be collected, processed, and reported as necessary for the purpose of the trial according to the study protocol.

Some of the blood samples will be analysed in the hospital's laboratory and are part of the patient's routine care. When the results are available, the samples will be destroyed according to the hospital's regulations.

Some of the blood samples will be sent to external laboratories for analysis. To maintain confidentiality, these samples will be coded and will not contain any personal identifying information.

Two serum samples will be stored for the purpose of studying specific characteristics predicting whether individual patients have a better or worse chance to respond to the treatment. Since these markers are still under investigation, we may need to do further research with these samples once the trial is finished. The samples will be kept in a secure place for a up to 5 years and will be destroyed when the investigated results become available. Unused blood samples from external laboratories described above, may be used for exploratory analyses and will be treated accordingly.

One blood sample for exploratory pharmacogenetic analyses will be kept in a secure place, for a up to 5 years and will be destroyed when the investigated results become available. The blood samples for DNA analysis will be double coded (two independent coding steps).

13 ADVERSE EVENTS

13.1 Adverse Events

Safety will be determined by an evaluation of physical examination, vital signs, ECG parameters, laboratory tests and by the occurrence of Adverse Events (AEs).

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. Events occurring prior to the first administration are part of baseline information.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

Adverse reaction (AR): All untoward and unintended responses to an IMP related to any dose administered.

All adverse events judged by either the reporting investigator or sponsor as having a reasonable suspected causal relationship to an investigational medicinal product are qualified as adverse reactions. The expression reasonable causal relationship means that there is evidence or argument to suggest a causal relationship.

Multiple signs or symptoms: If an AE consists of several signs or symptoms that can be represented by one single syndrome or diagnosis, the syndrome or diagnosis will be recorded in the CRF as the AE instead of the individual signs or symptoms.

Worsening: Signs, symptoms, syndromes or diagnoses present before the first administration of the IMP will be considered as AEs if they worsen after the start of the IMP.

AE collection: The condition of the patients will be monitored throughout the study from the time of signed Informed Consent up to the end of the study (day 28). The investigator will collect the AEs reported spontaneously, observed, or elicited in response to a non-leading question (for example, "How have you been feeling since we last asked you?"). The investigator will record all AEs in the source records and the eCRF.

Study specific definition:

Clinical events related to severe sepsis or sepsis complications are recorded on the appropriate eCRFs (see section 12.9). When serious, these clinical events are exempt from serious adverse event reporting, unless the investigator deems the event to be related to the administration of the study drug. The following events will be considered clinical events related to severe sepsis or sepsis complications:

- Death related to severe sepsis, that is, related to severe sepsis or a sequela of sepsis based on the interpretation of the investigator.
- Cardiovascular events: the need for vasoactive drugs, hypotension.
- Respiratory events: decreased PaO_2/FiO_2, 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 LFTs.
- 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.
- Systemic inflammatory response syndrome related criteria: tachypnea, hypopnea, leukocytosis, leukopenia, hypothermia, hyperthermia, tachycardia, or bradycardia.

AE rating:

The assessment of intensity of an AE will be made using the following general categorical descriptors:

Mild	No interference with the patient's daily activities and does not require mandatory corrective/symptomatic treatment

Moderate	Moderate interference with the patient's daily activities and/or requires minimal medical intervention or corrective treatment required
Severe	Major and unacceptable interference with the patient's daily activities and requires mandatory corrective/symptomatic treatment, possible hospitalisation

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** or **unrelated** to the IMP.

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

Unrelated	Clearly and incontrovertibly due only to extraneous causes, and does not meet criteria listed under unlikely, possible or probable.
Unlikely	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.
Possible	Follows a reasonable temporal sequence from administration of the IMP, and/or a causal relationship cannot be excluded and remains likely.
Probable	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 withdrawn, dosing interrupted, dose not changed, not applicable. AEs requiring therapy will be treated with recognised 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 hospitalisation or prolongation of existing hospitalisation,
- 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 hospitalisation may be considered as a SAE when, based upon appropriate medical judgement, it may jeopardise 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, the patient should be withdrawn from study, but closely followed-up during the entire course of the pregnancy and postpartum period.

Investigational Product Complaints: Pharmaceutical technical complaints associated with the investigational product must be reported immediately. The same reporting timelines as for SAEs apply.

13.2.3 Reporting of Serious Adverse Events

If any SAE occurs, the investigator will take appropriate action immediately and will strive to identify the causes 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 e-mail or fax to:

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

Stragen Services acknowledges the receipt of the SAE information by email to the investigational site within one working day. In the absence of email acknowledging the receipt or in case of issue in sending the fax or email, the investigator shall contact Stragen Services by any means for ensuring the receipt of SAE information at the earliest opportunity.

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 accompany the SAE form 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 immediate (ANSM)/within 7 days expedited reporting to the Competent Authorities and Ethics Committees.

SUSARs will be notified to the Competent Authorities and to the relevant ECs by Stragen Services immediately (ANSM)/within 7 days (other Competent Authorities) (for fatal and life-threatening SUSARs) or 15 days (all other SUSARs), with follow-up information in the following 8 days. The decision on the reportability will be made by the sponsor.

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, such as any new fact including information which may alter the current benefit–risk assessment of the IMP or the concerned clinical trial, which may lead to changes in the use of the IMP, in the conduct of the clinical trial, or of its related documents including the study protocol, or which may lead to suspend or terminate this clinical trial or similar researches, which may alter the current benefit–risk assessment of the IMP will be reported by the Sponsor (or delegate) immediately (France) or on an expedited basis to Health Authorities, Ethics Committees and the Investigators.

The specific reporting modalities implemented by French Decree number 2016-1537 dated 16 November 2016 for clinical trials involving healthy/patient volunteers are applicable for all parts of this study.

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 (treatment required or dose adjustments 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.

Findings and values related to physical examinations and measurements of ECG, vital signs, (temperature, blood pressure, and heart rate) and laboratory parameters will be defined as AEs if they are considered clinically relevant deteriorations compared with screening values, as judged by the investigator.

13.4 Period of Observation

Adverse events (serious and non-serious) will be recorded and reported to the sponsor from the time of written informed consent to the end of study (Day 28).

Relevant changes to patient's status will be recorded until day 90.

14 QUALITY ASSURANCE AND QUALITY CONTROL

Monitoring and auditing procedures developed or endorsed by the Sponsor will be followed in accordance with GCP guidelines. Direct access to the on-site study documentation and medical records must be ensured.

14.1 Monitoring and Source Data Verification

All aspects of the study will be carefully monitored by the sponsor, or designee, for compliance with applicable government regulations with respect to Good Clinical Practice (GCP) and current standard operating procedures.

The monitoring of this study will be performed by the Sponsor's Monitor(s) or a designee in accordance with the principles of GCP as laid out in the International Conference on Harmonisation (ICH) "Good Clinical Practice: Consolidated Guideline".

The clinical monitor, as a representative of the Sponsor, has an obligation to follow the study closely. In doing so, the monitor will visit the Investigator and site periodically as well as maintain frequent telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff. Further details will be described in the SOM.

14.2 On-Site Audits and Inspections

Domestic and foreign regulatory authorities, the EC or IRB, and an auditor authorised by the Sponsor may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection provided that patient names are removed on the copies to ensure confidentiality.

In case the study site is patient to an inspection by regulatory bodies, the investigator will inform the sponsor promptly after the notification of such inspection.

15 STATISTICAL CONSIDERATIONS

The analysis of study data will be detailed in a separate statistical analysis plan (SAP). Some of the analyses may be reported separately as specified in the SAP.

15.1 Statistical Methods

15.1.1 General Considerations

The analysis will be computed with SAS Version 9.4 (Copyright© 2013 by SAS Institute Inc., Cary, NC, USA).

Unless otherwise specified, baseline is defined as the last planned assessment prior to first dosing and no subgroup analysis is currently planned.

Missing safety, pharmacodynamic, pharmacokinetic and clinical data will not be replaced and will be treated as missing from summary and statistical analyses.

Unless otherwise specified, all treatment comparisons will be two-sided and significance will be assessed at the 5% level.

All safety, pharmacokinetic, pharmacodynamic and clinical data will be summarised by treatment group (Placebo, Dose level 1, Dose level 2 and Dose level 3), and visit, as appropriate.

Qualitative variables will be presented using the number of patients, the number of missing values, the frequency and the percentage per modality.

Quantitative variables will be reported using the number of patients, the number of missing values, the mean, the standard deviation, the median, the first and the third quartiles, the minimum and the maximum.

Between groups comparisons are calculated using an independent t-test or ANOVA-test for quantitative variables with a parametric distribution, or Mann-Whitney test or Kruskal Wallis-test for variables with a non-parametric distribution.

Data is tested for normality using Kolmogorov-Smirnov-test.

15.1.2 Analysis Sets

Safety analyses will be conducted on the safety analysis set, including all patients who received at least one dose of the study drug.

Pharmacodynamic (PD) analyses will be conducted on the PD analysis set, including all patients who received at least one dose of study drug, had at least one post-baseline PD assessment and no protocol deviation with a major effect on PD results.

Pharmacokinetic (PK) analyses will be conducted on the PK analysis set, including all patients who received at least one dose of MOTREM, had at least one post-baseline PK assessment and no protocol deviation with a major effect on PK results.

15.1.3 Endpoints

Safety and tolerability will be the primary endpoint and it will be monitored during the course of the study as specified below:

<u>Safety and Tolerability Parameters</u>

- Vital signs: systolic (SBP) and diastolic (DBP) blood pressure, heart rate, and body temperature.
- ECG (12-lead ECG)
- Safety laboratory tests: haematology, coagulation, plasma biochemistry.
- Presence of anti-LR12 antibodies
- Adverse events: from screening until study completion.

Secondary endpoints include the following:

Pharmacokinetics

Plasma concentrations of LR12 will be measured by a validated LC-MS/MS assay and analysed using non-compartmental methods to obtain estimates of the PK parameters.

Pharmacodynamics (exploratory)

The concentration profiles of biomarkers (sTREM-1, immune and vascular related biomarkers) over time and biomarker mRNA levels will be analysed.

Clinical Parameters

- Resolution of organ dysfunction (SOFA score total and individual domains)
- Vasopressor use
- Invasive mechanical ventilation
- Renal support
- Time until shock reversal defined as cessation of vasopressor support for 24 hours
- Mortality at day 28 and day 90

Safety and tolerability will be the primary endpoint and in addition, the exposure of MOTREM will be analysed. The biomarker concentration profiles over time and the area under the concentration (AUC) curves will be analysed as secondary PD variables.

The MOTREM concentration profile over time and the main derived PK parameters will be analysed as PK endpoints.

The endpoints and their analysis will be further specified in the statistical analysis plan (SAP).

15.1.4 Baseline Characteristics and Patient Disposition

Baseline characteristics (medical history, previous therapies, APACHE II Score, physical examination and serum pregnancy test), demographics and disposition data will be summarised by treatment group (Placebo, Dose level 1, Dose level 2 and Dose level 3).

15.1.5 Safety Analyses

Adverse events will be coded using the MedDRA dictionary version 18.1 or higher. Treatment emergent adverse events (events start after the first dose of investigational treatment or events present prior the administration of investigational treatment and worsened during the study (increased in severity)) will be classified by primary system organ class, preferred term and treatment group. Separate summaries will be performed for study medication related events, death, serious adverse events, adverse events leading to discontinuation of study medication and other adverse events of interest.

Other safety parameters that will be assessed include safety laboratory parameters (haematology, coagulation, biochemistry, arterial blood gases etc), vital signs (SBP, DBP, heart rate and body temperature), ECG and exposure of MOTREM. The parameters will be listed by treatment group (Placebo, Dose level 1, Dose level 2 and Dose level 3), patient and visit and summarised using standard descriptive statistics. All abnormal values will be identified in patient data listings. Changes from baseline will be described.

PD Analyses: Pharmacodynamic data will be listed by treatment, patient, and visit/time. Summary statistics will be provided by treatment and visit/time. Geometric means and CV will be presented for the primary and secondary PD endpoints.

PD endpoints will be compared between treatments with an ANOVA on logs. Each MOTREM dose group will be compared to placebo with a contract t-test at the 2-sided 10% level.

PK Analyses: Observed MOTREM serum concentrations will be summarised by treatment and corresponding time when sampling occurred. Derived PK parameters will be summarised by treatment.

Clinical Analyses: Several clinical parameters as the clinical events related to sepsis and its complications, the SOFA score total and each sub-score (respiratory, cardiovascular, hepatic, coagulation, renal and neurological system), the vasopressor use, the mechanical ventilation and intubation will be described by treatment group and visit. Standard descriptive statistics will be used.

15.2 Determination of Sample Size

A formal sample size calculation was not performed for the primary objective of the study. Instead, the sample size 48 patients overall (N=12 for each dose level) was chosen to provide sufficient data for this pilot study of MOTREM in patients with septic shock. This is in line with recommendations for sample size of pilot studies (23).

As this is an exploratory study no adjustments for multiplicity will be employed.

15.3 Randomisation Methods

The randomisation lists will be performed by Ascopharm Statistician using SAS software Version 9.4 (Copyright© 2013 by SAS Institute Inc., Cary, NC, USA) with the procedure "PROC PLAN" before the start of the study.

Randomisation lists produced will be implemented into the randomisation module of the Ennov Clinical© software (V7.5 or higher).

The first randomisation list for the stage 1 will be created with a minimum of 3 randomisation blocs of 4 i.e. 12 patients. Each sequential cohort (0.3, 1.0 and 3.0 mg/kg/h of MOTREM) will contain 4 patients (3 active and 1 placebo). Patient satisfying eligibility criteria will be randomised in a 3:1 ratio per cohort to the treatments as specified below:

- MOTREM
- Placebo

The second randomisation list for the stage 2 will be created with a minimum of 9 randomisation blocs of 4 i.e. 36 patients. Each dose group will contain 9 patients. Patient satisfying eligibility criteria will be randomised in a 1:1 ratio to the treatments as specified below:

- Dose level 1
- Dose level 2
- Dose level 3
- Placebo

For security, the two randomisation lists will be extended over the number of patients initially planned. For example, for the stage 1, three extra cohorts of 4 patients each will be planned as cohorts could be repeated once.

A randomisation list will be provided to the site's pharmacy, who is in charge of blinding and labelling of the treatments.

15.4 Interim Analysis

One unblinded interim analysis of complete 28-Day data is planned, after the end of study visit (D28) is complete for all patients, while the study is still ongoing. Some exploratory biomarker and ADA data may not be included in the interim analysis.

The study will be unblinded after the last subject completes the EOS visit and the interim database is available, including cleaned and locked data up to EOS visit (except possibly some of the biomarkers/ADA results). All parties (sponsor, investigators and subjects) may be unblinded at the time of this interim analysis.

The purpose of this interim analysis is to gather preliminary information in order to trigger possible external business decisions. The study will not be stopped early on the basis of this interim review.

Details for this interim analysis will be specified in the statistical analysis plan (SAP). The SAP will be finalised prior to unblinding.

15.5 Retrospective Collection of Data and Post-hoc Analysis

For exploratory analyses of nangibotide's efficacy for the treatment of septic shock, additional data will be collected on the following parameters:

- SOFA score: For all surviving patients, SOFA scores will be collected up to day 5. The purpose of this is to replace data that have been treated as missing in the original analysis.
- Duration of ICU stay: This is expected to provide efficacy data on a clinically relevant endpoint.

These data have not been collected in the original eCRF. They will be collected from source data at sites to the extent available.

The analysis of this data will follow the principles of the main analysis and will be further specified in a separate statistical analysis plan. The results will be reported separately.

16 ETHICAL AND LEGAL ASPECTS

16.1 Good Clinical Practice (GCP)

This protocol complies with the principles of the World Medical Assembly (Helsinki 1964) and subsequent amendments (24) 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 written 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. Signed ICFs must remain on file and must be available for verification by Study Monitors at any time. Another signed original of the ICF must be given to the patient or the patient’s legally authorised 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
- If the family cannot be reached, an emergency informed consent procedure will be followed

- 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 Ethics Committee (EC) approved consent forms, and a copy of the EC 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 and regulatory authority approval. 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. The appropriate documents will also be submitted to the 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, 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.

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

If applicable, the ECs 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. This also applies to any communication between the (coordinating) investigator or sponsor's delegate and the authorities.

16.5 Ongoing Information for Ethics Committee

Unless otherwise instructed by the EC 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 CSP. 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 regulatory agency and by the Sponsor or investigator to the EC as required by local regulation or by the EC.

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 have to 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 has to be transferred to another person (e.g. other investigator). The Sponsor has to 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 authorised to entry data in the eCRF. They are identified using a login and a password as an electronic signature. 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 and randomised. Any additional information on data entry process will be included in a data handling procedure. The investigator must check that all the data is accurate and correct. If any information is not applicable, missing (not determined) or unknown, the investigator will record "NA", "ND" or “UK” in the appropriate place. After a page/screen is completed, the investigator has to validate it (lock action). This action prevents from modification of the data after entry (data are “frozen”).

If a data that has already been validated in the eCRF has to be corrected, the initial value, the identity of the person who modify the data, the date and the reason of the modification are tracked in an audit trial file, linked to the eCRF, not accessible/not modifiable to/by the investigators. When, the correction is done; the investigator has to validate it.

Each opened case report form must be completed. After final verification by the monitor and resolution of possible queries, the data are definitively not modifiable by the investigator.

17.2 Clinical Database

Data Management will create the database under Oracle (V10.2.04 or higher) and the eCRF entry screens.

The eCRF application will be accessible by connecting on a dedicated and secure website using Clinsight Online module. Each user will connect by using personal identifier / password.

The Data Manager will write the Data Handling Manual (DHM) which describes the various data management steps, the database structure (name and format of the items) and the annotated eCRF, and the validation plan.

The investigator, sub-investigators or its designated representative will enter the data for each patient on online eCRF application. The data will be extracted from the ORACLE database and formatted as SAS files (V9.4).

The Data Manager will program the consistency checks defined in the validation plan. These checks will result in the production of Electronic Data Clarification Forms (eDCFs). The investigator or designated representative will directly answer to these eDCFs on the eCRF application.

Adverse events will be coded using MedDRA dictionary, and concomitant treatment will be coded using WHO-DRUG dictionary version 2015-3 or higher.

At the end of the validation process, the Data Manager will produce listings which describe all protocol deviations. The status of these deviations (minor or major) will be discussed during the pre-analysis review, and the analysis population will be defined.

At the end of the data management process, the database will be frozen and the SAS files will be sent to INOTREM SA according to the Data transfer process.

17.3 Use of Study Findings

All information concerning the product as well as any matter concerning the operation of the Sponsor, such as clinical indications for the drug, its formula, methods of manufacture and other scientific data relating to it, that have been provided by the Sponsor and are unpublished, are confidential and must remain the sole property of the Sponsor. The investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the Sponsor is obtained.
The Sponsor has full ownership of the original eCRFs completed as part of the study.

By signing the clinical study protocol, the investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. The authorities will be notified of the investigator's name, address, qualifications, and extent of involvement.
All materials, documents and information supplied by the Sponsor to the investigator, and all materials, documents and information prepared or developed in the course of the study to be performed under this protocol, shall be the sole and exclusive property of the Sponsor.

17.4 Clinical Study Report

The Sponsor will document the findings of the study in a clinical study report final report according to applicable legal requirements and regulations.

As required by local regulation or by the EC or IRB, a summary of the clinical study will be submitted by the Sponsor to the regulatory authorities and by the Sponsor or investigator to the EC or IRB.

The following exploratory study assessments will be reported separately:

- RNA transcriptomics
- Pharmacogenetics

17.5 Confidentiality

After patients have consented to take part in the study, their medical records and the data collected during the study will be reviewed by the sponsor and/or its representatives. These records and data may, in addition, be reviewed by the following: (i) independent auditors who validate the data on behalf of the sponsor; (ii) national or local regulatory authorities.

Although patients will be known by a unique number, their date of birth will also be collected and used to assist the sponsor to verify the accuracy of the data, for example, that the results of study assessments are assigned to the correct patient. 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 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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APPENDIX 1: RECOMMENDATIONS FOR FLUID THERAPY

The following measures of fluid therapy are recommended according to the current treatment guideline of the Surviving Sepsis Campaign (9):

1. Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock
2. Against the use of hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock
3. Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids
4. Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients
5. Fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (e.g., change in pulse pressure, stroke volume variation) or static (e.g. arterial pressure, heart rate) variables

APPENDIX 2: LIST OF NOT ALLOWED IMMUNOSUPRESSIVE DRUGS

Immunosuppressive agent	**Upper limit dosage, use**
Corticosteroid Prednisone Hydrocortisone Methylprednisolone Dexamethasone Cortisone Betamethasone	>10 mg/day of prednisone or its equivalent daily 10 mg 40 mg 8 mg 1.5 mg 50 mg 1.2 mg
Methotrexate (Rheumatrex, Trexall)	Excluded at any dose
Leflunomide (Arava)/ Teriflunomide (Aubagio)	Acceptable if being used as monotherapy
Thalidomide	Patients receiving this drug within the past 72 hours are excluded
Biologics	
Anti-tumor necrosis factor (TNF) agents Etanercept (Enbrel) Adalimumab (Humira) Infliximab (Remicade) Certolizumab (Cimzia) Golimumab (Simponi)	Patients receiving anti-TNF agents within the past 8 weeks are excluded.
Interleukin-1 Receptor antagonist (IL-1 RA) (Kineret)	Patients receiving IL-1 RA within the past 8 weeks are excluded
CTLA-4 Fusion protein Atapacept (Orencia) Belatacept (Nulojix)	Patients receiving CTLA-4 Fusion protein within the past 8 weeks are excluded.
Anti-CD20 e.g. Rituximab (Rituxan/MabThera) Obintuzumab (Gazyva)	Patients receiving this drug within the past 3 months are excluded.
Anti-CD52 Alemtuzumab (Campath)	Patients receiving this drug within the past 3 months are excluded.
Anti-IL2 Daclizumab or Anti-Tac (Zenapax)	Patients receiving this drug within the past 3 months are excluded.
Anti-IL6 Tocilizumab (Actemra/RoActemra)	Patients receiving this drug within the past 3 months are excluded.
Anti-IL12/13 Ustekinumab (Stelara)	Patients receiving this drug within the past 3 months are excluded
Anti-BAFF (B-cell activating factor) Belimumab (Benlysta)	Patients receiving this drug within the past 3 months are excluded.
Integrin inhibitor Natalimumab (Tysarbi)	Patients receiving this drug within the past 3 months are excluded.