16.1 STUDY INFORMATION

16.1.1 Protocol and Protocol Amendments

- Final Study Protocol (Version 03, 13 May 2016)
- Amendment 2 (03 May 2016)
- Amendment 3 (12 May 2016)
- Amendment 4 (22 July 2016)

STUDY PROTOCOL

Including Amendments 1-3

A Phase I, randomised, placebo controlled study to assess the safety, tolerability and pharmacokinetic profiles of ascending, single, intravenous doses of MOTREM (LR12) in healthy male subjects

Investigational medicinal product: MOTREM (LR12)
Development phase: Ia

Version: 3.0 Final
Date: 13 May 2016

Sponsor Study Code:	MOT-C-104
CRO Study Code	C15030
EudraCT Number	2015-005654-35
Sponsor	INOTREM SA 114 Rue La Boétie 75008 Paris, France
Sponsor's Officer	Jean-Jacques GARAUD, MD Chief Executive Officer 114 Rue La Boétie 75008 Paris, France
Principal Investigator	Dr Ulrike Lorch, MD FRCA FFPM Richmond Pharmacology Ltd. St George's University of London Cranmer Terrace, Tooting London SW17 0RE, UK
Study Site	Richmond Pharmacology Ltd. Croydon University Hospital, Thornton Wing, 530 London Road, Croydon, CR7 7YE, UK

HISTORY OF CHANGES

The following changes to the second version of the study protocol (22 FEB 2016) were implemented with study protocol amendment 3. These changes are non-substantial.

- Reduction of the number of PK samples in line with the adaptive feature no 13 Limit I & II.
- Correction of minor errors
- Administrative change (provider for PK analysis): Dynakin was replaced by Phinc.

The following changes to the second version of the study protocol (22 FEB 2016) were implemented with study protocol amendment 2. These changes are non-substantial. A new version of the study protocol was not issued for this amendment.

- 100% extension of Group 2 (Part A) in line with the Adaptive feature no 8, Limit I-III. This was made to gather additional pharmacokinetic information.

The following changes to the first version of the study protocol (19 JAN 2016) were implemented with study protocol amendment 1. These changes are non-substantial.

- Addition of exclusion criterion to exclude volunteers with pregnant partners due to the request oft he ethics committee
- Clarification of vital signs measurements
- Clarification of holter ECG measurements

1 PROTOCOL APPROVAL SIGNATURES

1.1 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	Date:	Signature:
Jean-Jacques GARAUD, MD, INOTREM	19 May 2016	

Project Manager	Date:	Signature:
Valérie CUVIER, INOTREM	18 May 2016	

Study Statistician	Date:	Signature:
Aude Lasfargues ASCOPHARM Groupe NOVASCO	19 May 2016	

1.2 Investigator's Agreement

I have read this INOTREM SA Protocol No. MOT-C-104

A Phase I, randomised, placebo controlled study to assess the safety, tolerability and pharmacokinetic profiles of ascending, single, intravenous doses of MOTREM (LR12) in healthy male subjects

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 subject in order to obtain consent.

I agree to conduct this trial according to this protocol and to comply with its requirements, subject 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

Principal Investigator Date: Signature:

Dr Ulrike Lorch, MD FRCA FFPM

2 STUDY PERSONNEL

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3 TABLE OF CONTENTS

List of Tables

List of Figures

4 LIST OF ABBREVIATIONS

γGT : Gamma glutamyl transpeptidase
ADA : Anti-Drug Antibody
AE : Adverse event
$Ae_{(0\text{-}24h)}$: Cumulative amount excreted in urine from time 0 to time 24 h
ALAT : Alanine amino transferase
ALP : Alkaline phosphatase
API : Active Pharmaceutical Ingredient
aPTT : activated Partial Thromboplastin Time
ASAT : Aspartate amino transferase
ATC : Anatomic Therapeutic Class
$AUC_{(0\text{-}8h)}$: Area under the plasma concentration-time curve from time 0 to time 8 h
$AUC_{(0\text{-}t)}$: Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
$AUC_{(0\text{-}inf)}$or $AUC(0\text{-}\infty)$: Area under the plasma concentration time curve extrapolated to time infinity
AR : Adverse reaction
BMI : Body mass index
bpm : beat per minute
CL : Plasma clearance
$C_{0.25h}$: Concentration at the end of the loading infusion
C_{8h} : Concentration at the end of the maintenance infusion
C_{max} : Maximal plasma concentration
Cox-1 / 2 : Cyclo-oxygenase 1/ 2
CPK : Creatine phosphokinase
CRF : Case report form
$C_{ss\ inf}$: Steady state concentration during the maintenance infusion
CV : Coefficient of variation
DBP : Diastolic blood pressure
DHP : Data Handling Protocol
EC : Ethics Committee
ECG : Electrocardiogram
FIH : First in Human
h : hour(s)
HBsAg : Hepatitis B surface antigen
HCV : Hepatitis C virus
HED : Human Equivalent Dose
HIV : Human immunodeficiency virus
HR : Heart rate
IL : Interleukin
IMP : Investigational medicinal product
iNOS : inducible Nitric Oxide Synthase
INR : International Normalised Ratio
ITT : Intent-to-treat
i.p. : intraperitoneal
i.v. : intravenous
IWRS : Interactive Web Randomisation System
K_{inf} : Infusion rate
LPS : Lipopolysaccharide
LR12 : 12 amino-acid peptidic fragment of sTLT-1
LSLV : Last Subject Last Visit

λ_z : Terminal elimination rate
MCHC : Mean corpuscular haemoglobin concentration
MCV : Mean corpuscular volume
MedDRA : Medical dictionary for regulatory activities
MHC : Mean haemoglobin concentration
MOTREM : Investigational Medicinal Product (formulation of the active ingredient LR12)
MTD : Maximum tolerated dose
MS : Mass Spectrometry
NOAEL : No-observed-adverse-effect level
PK : Pharmacokinetics
QTcB : QT corrected Bassett:
QTcF : QT corrected Fridericia
SAE : Serious adverse event
SAS® : Statistical analysis system
SBP : Systolic blood pressure
SD : Standard deviation
SOC : System organ class
SOM : Study Operations Manual
SRC : Safety Review Committee
SUSAR : Suspected Unexpected Severe Adverse Reaction
$t_{1/2}$: Terminal elimination half life
T° : Temperature
TEAE : Treatment-emergent adverse event
TLRs : Toll-like Receptors
TLT-1 : TREM-Like Transcript-1
TREM-1 : Triggering receptor expressed on myeloid cells 1
t_{max} : Time at which the plasma concentration maximum occurs
USP : U.S. Pharmacopeial Convention
Vd : Volume of distribution (CL/λ_z)

5 STUDY SYNOPSIS

Protocol No. MOT-C-104 **Study Drug:** MOTREM (LR12)

Title of the Study:

A Phase I, randomised, placebo controlled study to assess the safety, tolerability and pharmacokinetic profiles of ascending, single, intravenous doses of MOTREM (LR12) in healthy male subjects

Principal Investigator:

Dr Ulrike Lorch, MD FRCA FFPM

Study Centre:

Richmond Pharmacology Ltd.

St George's University of London, Cranmer Terrace, Tooting, London, SW17 0RE, UK

Croydon University Hospital, Thornton Wing, 530 London Road, Croydon, CR7 7YE, UK

Study Period:

- First enrolment expected: February 2016
- Completion date expected: June 2016

Clinical Phase: Ia

(The study does not have therapeutic or prophylactic intent and does not plan to assess efficacy)

Objectives:

Primary

- To assess the safety and tolerability of MOTREM (LR12) in comparison with placebo, after single intravenous (i.v.) dose administration in healthy young male subjects

Secondary

- To assess the pharmacokinetics (PK) of MOTREM (LR12) after single i.v. dose administration in healthy young male subjects.
- To investigate the presence of anti-MOTREM (LR12) antibodies after single i.v. dose administration in healthy young male subjects.

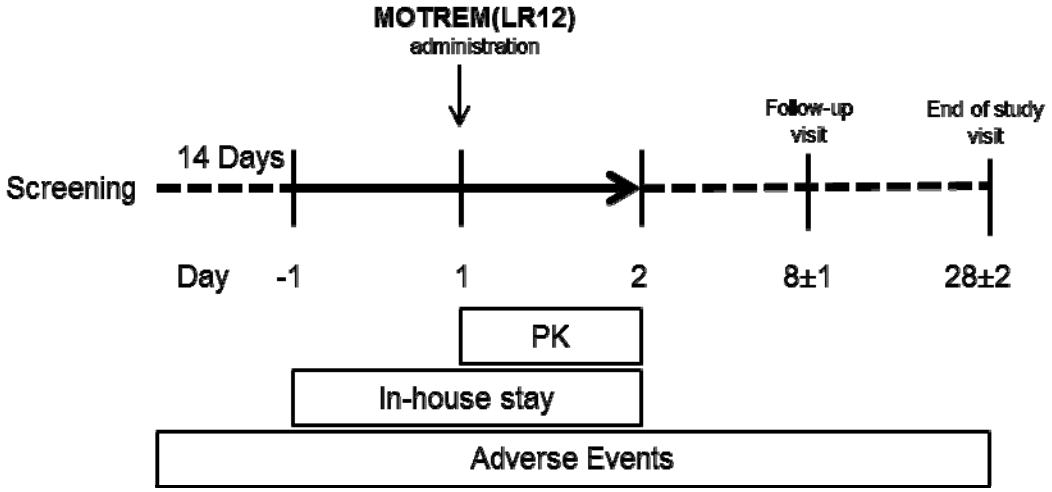
Study Design:

This study is a single center, randomised, placebo-controlled (Part B) with sequential i.v. dose escalation groups design.

Single doses of MOTREM (LR12) or matching placebo (Part B) are planned to be administered following a sequential group design in 26 healthy young male subjects aged from 18 to 45 years: Part A (Groups 1 and 2 of 1 subject) followed by Part B (Groups 3 to 8 of 4 subjects each). For Part A (Groups 1 and 2), one subject each will receive MOTREM. For Part B (Groups 3 to 8) 3 subjects will receive MOTREM and 1 subject will receive placebo (3:1 ratio). Dose escalation to the following scheduled dose will only occur after satisfactory review of all safety and tolerability data by the Safety Review Committee in accordance with Table 1, protocol sections 8.2 Rules for dose escalation/progression and 8.3 Toxicity rules.

Subjects will be screened within 14 days and screening may be performed over multiple days prior to entering the study on Day -1. Each subject will receive verbal and written information followed by signing of the Informed Consent Form (ICF) prior to any screening procedures taking place. Subjects will be admitted on Day-1. All the subjects from Part A (Groups 1 and 2) and Part B (groups 3 to 8) will be discharged on Day 2 after 24h post-dose (start of infusion). They will attend the unit for a follow-up visit on Day 8±1. The End of Study visit will take place on Day 28±2. All the assessments performed during the study are detailed in the Study Plan (Table 2 and Table 3). Study design features as well as number of subjects may be adapted according to Table 1.

Study Flowchart:



Number of Subjects:

26 subjects are planned (i.e. 2 first groups of 1 healthy male subject each and 6 groups of 4 healthy male subjects). Dose groups may be amended in accordance with Table 1 to collect relevant data. The total number of subjects will not exceed 72 subjects.

Diagnosis and Main Criteria for Admission:

Subjects will be included if they are healthy male, ≥18 to ≤45 with a BMI between 18-30 kg/m² inclusive having freely given their written informed consent to participate.

Main exclusion criteria are: any clinically relevant acute or chronic diseases which could interfere with the subjects' safety during the trial, or expose them to undue risk, or which could interfere with the study objectives. Any history of drug or alcohol abuse or clinical significant disease as determined by medical history, physical examination or other evaluations.

Part A:

Group 1: 1 mg (loading dose) over 15 minutes i.v.;

Group 2: 10 mg (loading dose) over 15 minutes i.v.;

Part B:

Group 3: 0.5 mg/kg i.v. loading dose and 0.03 mg/kg/h maintenance dose i.v. over 7 hours and 45 min;

Group 4: 1 mg/kg i.v. loading dose and 0.1 mg/kg/h maintenance dose i.v. over 7 hours and 45 min;

Group 5: 2 mg/kg i.v. loading dose and 0.3 mg/kg/h maintenance dose i.v. over 7 hours and 45 min;

Group 6: 5 mg/kg i.v. loading dose and 1 mg/kg/h maintenance dose i.v. over 7 hours and 45 min;

Group 7: 5 mg/kg i.v. loading dose and 3 mg/kg/h maintenance dose i.v. over 7 hours and 45 min;

Group 8: 5 mg/kg i.v. loading dose and 9 mg/kg/h maintenance dose i.v. over 7 hours and 45 min.

Please refer to Table 1.

Reference Treatment(s) and Mode of Administration:

Placebo solution: saline; i.v. administration

Anticipated Duration of Treatment:

Single dose administration.

Part A (Groups 1 and 2): 15 minutes i.v. dose

Part B (Groups 3 to 8): 7 hours and 45 minutes continuous i.v. administration after a 15 minutes i.v. loading dose.

Criteria for Evaluation:

Please refer to the Study Plan (Table 2 and Table 3) for detailed timing of the evaluations.

Safety Parameters:

- Vital signs: systolic (SBP) and diastolic (DBP) blood pressure, heart rate, and body temperature (tympanic).
- ECG (12-lead ECG, telemetry and Holter)
- Physical examination.

- Safety laboratory tests: haematology, coagulation, plasma biochemistry, urinalysis.
- Local tolerability at the infusion site.
- 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 non-compartmental methods to obtain estimates of the following PK parameters:
C_{max}, t_{max}, $C_{0.25h}$, C_{8h}, $C_{ss\ inf}$, $AUC_{0\text{-}0.25h}$, $AUC_{0\text{-}8h}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, $t_{1/2}$, λ_z, CL, Vd.

Statistical Methods:

Adverse Events:

Adverse events will be coded using the MedDRA dictionary version 17.1 or higher. They will be classified by System Organ Class and Preferred Term.

The number and percentage of subjects with at least one adverse event will be provided.

Analysis of treatment-emergent adverse events (TEAE)

TEAEs will be summarised and described for the following criteria:

- Number and percentages of subjects with at least one TEAE
- Number and percentages of subjects with at least one severe TEAE
- Number and percentages of subjects with at least one study treatment related TEAE
- Number and percentages of subjects with at least one serious TEAE
- Number and percentages of subjects with at least one TEAE leading to treatment withdrawal

The maximum intensity encountered during the evaluation period will be recorded.

The number of TEAEs of each category will also be provided by system organ class and preferred term.

Analysis of Deaths and Other Serious Adverse Events

A listing of deaths will be provided.

A summary table of the other serious adverse events should be provided. In case of a low incidence of serious adverse events, only a listing will be done.

Vital Signs, ECG, Physical Examination and Laboratory Data:

Vital signs (SBP, DBP, heart rate and body temperature), ECG (12-lead ECG, telemetry and Holter), physical examination and laboratory data will be described at each visit/time. Changes from baseline will be described. Abnormal values will be identified in subject's data listings.

Concomitant Treatments:

Concomitant treatments are coded using the WHO-DRUG dictionary version 2014-3. All treatments continued after the inclusion or appeared during the study will be summarised by Anatomical Therapeutic Class (ATC) and substance name.

Pharmacokinetics:

Individual and mean concentration versus time will be plotted on linear and semi logarithmic scales. Plasma concentrations and plasma PK parameters will be listed for LR12. Summary statistics of PK parameters including means, geometric means, medians, ranges, standard deviations, coefficients of variation will be presented for each dose.

Analysis of variance models will be applied to the dose normalised and logarithmically transformed pharmacokinetic parameters to investigate possible deviations from dose proportionality

6 INTRODUCTION

MOTREM (formulated LR12) is developed for the treatment of sepsis and myocardial infarction. MOTREM is to be introduced into Phase I clinical studies to assess safety, tolerance, pharmacokinetics, and pharmacodynamic profile.

MOTREM is the formulation of the active ingredient LR12, which is a 12 amino-acid peptide prepared by chemical synthesis. The investigational drug product MOTREM is prepared as a stable lyophilised product of LR12 peptide in sodium citrate and arginine. The powder is to be solubilised with 40 mL of saline solution for injection to yield a clear and colourless solution of LR12 at 10 mg/mL and at pH 5.5.

The manufacturing of MOTREM for administration to humans is in compliance with the principles of good manufacturing practice (GMP).

MOTREM is expected to be administered as a continuous i.v. infusion in the critical care setting for an average duration of 3 to 5 days.

6.1 Mode of Action:

The Triggering Receptor Expressed on Myeloid Cells 1 (TREM-1) is an immunomodulatory receptor expressed on innate immune cells (1–4) 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”) (5), 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 inhibit the amplification of the immune response caused by the activation of TREM-1 both in sepsis and myocardial infarction (6,7).

6.2 Pharmacology:

In vitro, LR12 was shown to be a competitive inhibitor of TREM-1, able to inhibit TREM-1-induced activation of several intracellular proteins implicated in inflammation as well as cytokine production by human neutrophils and monocytes in a dose dependent manner. However, the in vitro incubation of LR12 alone with leucocytes in resting conditions did not induce the spontaneous activation of any of the studied intracellular signalling pathways.

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 decreased mortality with a strong reduction (not abrogation) of the inflammatory response markers, sepsis-induced tissue abnormalities and showed protective effects on the cardiovascular system. In a mini-pig model of peritonitis, the administration of LR12 led to a decreased need of vasopressor (norepinephrine) which translates to a substantial protective effect of the cardiovascular system. LR12 also prevented sepsis-induced tissue abnormalities and dysfunctions.

The TREM-1 signalling pathway belongs to the 10 most upregulated pathways during the "genomic storm" that can be observed in patients with septic shock. During experimental Monkey endotoxemia, the administration of LR12 attenuated the endotoxin-induced blood pressure decrease and release of several inflammatory cytokines in blood. The transcription of a wide range of genes related to the "genomic storm" was also attenuated by LR12 administration.

In addition, LR12 was evaluated in animal models of myocardial infarction: In a rat model of myocardial ischemia-reperfusion, treatment with LR12 reduced the ventricular dilation and improved systolic and diastolic ventricular functions. In a mini-pig model of cardiogenic shock, treatment with LR12 was linked to a strong protection of the cardiovascular system and decreasing the infarct size.

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

6.3 Rationale for Conducting Study

The aim of this First-in-Human (FIH) study is to obtain information on the safety, tolerability and pharmacokinetics of single ascending doses of MOTREM in healthy young male subjects.

The rationale for taking MOTREM into further development is the expectation that this compound could be an effective new anti-sepsis therapeutic agent. Prior to initial testing in patients, the safety and the pharmacokinetic characteristics of the drug in healthy humans must be investigated.

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 healthy subjects purely for research and development purposes and those subjects receiving IMP will experience no medical benefit except for a general health examination.

6.4.2 Potential Risks

6.4.2.1 Nonclinical Safety Pharmacology and Toxicology:

Toxicity studies were only conducted in one species in accordance with ICH guidance documents S6(R1) and M3(R2) as well as to EMA's guidance on repeated dose toxicity (EMEA/CHMP/SWP/488313/2007). Safety pharmacology also followed the ICH S7A and S7B guidance.

A cardiovascular safety study in Cynomolgus monkeys did not identify any adverse cardio¬vascular effect of LR12, when administered as an intravenous infusion of 18-times the expected pharmacologically active dose. In addition, the central nervous and pulmonary systems were explored during the toxicity studies and did not unveil untoward effects.

Receptor binding assays with a wide range of receptors did not show any relevant off target effects in vitro.

A bacterial reverse mutation test (Ames test) and a chromosome aberration test did not show any evidence for genotoxicity of LR12.

Toxicokinetic studies showed dose-dependent kinetics and suggested a clearance of the product within 15 to 30 minutes depending on the dose.

A series of toxicity studies was conducted with LR12 in cynomolgus monkey, as this represents the only relevant species. In the pivotal 14-day toxicology study with the clinical formulation, the administration of LR12 was safe and well tolerated at doses 7.2, 24 and 140 mg/kg/day. No adverse events were observed up to the highest dose level. In addition, a dose of 440 mg/kg/day in a preliminary formulation was found to be safe and well tolerated in a 14-day study.

Severe time dependent adverse events, likely related to immunogenicity, were observed in the low- dose arm of an early toxicity study conducted with an experimental frozen formulation that was diluted with a technical, non USP grade buffer. Further toxicology studies with a suitable buffer or the API alone and with the final clinical formulation did not reproduce these findings.

6.4.2.2 Clinical Studies

There is currently no clinical experience with MOTREM. Potential risks will be closely monitored for as part of the safety evaluations being performed in this study.

Measures to minimise the risks to volunteers will include:

- Selection of a starting dose well below a dose level for which effects are expected Please refer to protocol section 8.4.1.
- Sentinel dosing of subjects. Please refer to protocol section 8.4.4.
- Progression to next dose level only after evaluation of data from previous groups/cohorts and approval from Safety Review Committee (SRC). Please refer to protocol section 8.2.3 and 8.2.4.
- Clinical and laboratory monitoring of study subjects. Please refer to protocol section 8.2.2 and 12.1.2.
- Exposure to study drug limited to 8 hours. Please refer to protocol section 8.4.1.

6.4.2.3 Allergic Reactions, Infusion Reactions and Anaphylaxis

As with all protein products, administration of MOTREM may result in hypersensitivity reactions including anaphylaxis, or infusion site associated reactions.

Subjects will be closely monitored during and after IMP administration for any symptoms of anaphylaxis and other hypersensitivity reactions, including circulatory and/or respiratory changes or arrest, or urticaria, arthralgia, myalgia or other signs of related reactions. Adequate treatment will be immediately available. Infusion-associated AEs may occur, and depending on its type and severity, discontinuation of infusion may be required. Subjects will be informed of early symptoms and signs of hypersensitivity reactions including hives, swollen face, eyelids, lips, or tongue, or trouble with breathing. An acute infusion reaction algorithm will be used to manage infusion related reactions (refer to Appendix 19.2). In this study regular assessments to monitor infusion reactions and infusion site reactions will be done.. A mandatory sentinel dosing strategy of dosing one subject on IMP on the first day will be used

for each cohort. If safety and tolerability is acceptable the remaining subjects of each cohort will be dosed in group sizes of no more than three with a minimum interval of 24 hours between the start of dosing in the first subject on the previous day and the start of dosing on the next day. In addition, during a dosing day, there will be a minimum interval of 60 minutes between the start of (maintenance) dosing in a subject and the start of dosing in the next subject to ensure that reactions can be dealt with promptly. Any reactions will be treated and taken into account in the dose progression/escalation and toxicity rules. If anaphylactic reactions occur the current "UK Treatment Guideline for Anaphylactic Reactions" of the UK Resuscitation Council will be followed (refer to Appendix 19.1).

6.4.2.4 Product-Specific Antibody Development

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 8 hours is not expected to result in triggering an immune response in the study subjects. However, the possibility of triggering an immune response against it in humans still exists. Therefore, all subjects will be carefully monitored for 28 days. Should any subject develop ADA against LR12, they will be followed up for at least 3 months or until the antibody response is no longer detected.

7 STUDY OBJECTIVES

7.1 Primary Objectives

- To assess the safety and tolerability of MOTREM in comparison with placebo, after single intravenous (i.v.) dose administration in healthy young male subjects.

7.2 Secondary Objectives

- To assess the pharmacokinetics of LR12 after single i.v. dose administration in healthy young male subjects
- To investigate the presence of anti-LR12 antibodies after single i.v. dose administration in healthy young male subjects

8 STUDY DESIGN

8.1 Overall Study Design and Procedure

This will be a First in Human (FIH), randomised, placebo-controlled study, with sequential single ascending intravenous dose groups. Single doses of MOTREM (LR12) or matching placebo are planned to be administered following a sequential group design in 26 healthy young male subjects aged from 18 to 45 years.

This study incorporates the use of an adaptive design (8). Study specific adaptive features and their limits are described in Table 1.

Dose escalation and progression will be limited by evaluation of safety and tolerability data governed by toxicity rules (Section 8.3) and will only occur after satisfactory review of all safety and tolerability data by the Safety Review Committee (Section 8.2.3).

Table 1. Adaptive Protocol Features.

Adaptive Study Design Areas	Features	Limits
Dose	1. All anticipated dose levels/dosing regimens in Parts A and B can be adjusted in accordance with PK, safety and tolerability data collected up to the decision making time-point.	I. The starting dose for Part A of the study will not exceed 1 mg. II. The maximum dose for Part A will not exceed 10 mg. III. The starting loading dose in Part B will not exceed 0.5mg/kg. IV. The starting maintenance dose in Part B will not exceed 0.03 mg/kg/h. V. The dose increments between the dose levels 1 to 2 in Part A will be no more than 10-fold. VI. The loading dose increments between the dose levels in Part B will be no more than 2.5-fold. VII. The maintenance dose increments between the dose levels in Part B will be no more than 3.5-fold.
	2. In Part B, the anticipated dosing regimens can be adjusted in accordance with PK, safety and tolerability data collected up to the decision making time-point. 3. The term dosing regimen includes (1) the dose level administered as loading dose, (2) the dose level administered as maintenance dose (3) the duration of the loading dose and (4) the duration of the maintenance dose. Accordingly, these can be adjusted individually or in combination.	I. The treatment duration will not exceed 8 hours. II. Minimum duration of loading dose will be of 15 min. III. Limits outlined under adaptive feature 1 apply.
Timing	4. Dosing regimens may overlap.	I. Protocol specific minimum study progression/escalation requirements for the SRC must be met before dose progression/escalation as described in section 8.2.
	5. Cohorts/dosing regimens may be split into sub-groups	I. A mandatory sentinel dosing strategy of dosing one subject on IMP on the first day will be used for each cohort. If safety and tolerability is acceptable the remaining subjects of each cohort will be dosed in group sizes of no more than three with a minimum interval of 24 hours between the start of dosing in the first subject on the previous day and the start of dosing on the next day. II. During a dosing day, there will be a minimum interval of 60 minutes between the start of (maintenance) dosing in a subject and the start of dosing in the next subject. III. Additional sentinel or sequential dosing for all cohorts and study parts can be performed at the discretion of sponsor

Adaptive Study Design Areas	Features	Limits
		and investigator.
Flexible Cohort Sizes	6. Withdrawn subjects can be replaced at the discretion of the sponsor and investigator, if not withdrawn for safety reasons. 7. Replacement subjects may be enrolled in an ongoing cohort, or dosed together as a group or dosed separately. 8. The number of subjects in a dose cohort can be extended to gather further information on a dosing regimen.	I. The maximum extension is 100% of the original group/cohort size at the selected dose level. II. The randomisation will follow the randomisation system of the originally planned dose cohort. [III. Study specific toxicity rules (Table 4) apply.
Optional Study Parts/Cohorts	9. Optional groups/cohorts may be included to explore additional dose levels and/or dosing regimen.	I. Up to 2 additional groups/cohorts may be included into each, Part A and B. II. The size of the optional groups/cohorts will not exceed the limits outlined under adaptive features 6-8.
Samples and Assessments	10. The in-house stay or follow-up period may be prolonged if: a. It is considered clinically necessary by the PI or delegate for individuals on a case-by-case basis. b. The Safety Review Committee (SRC) considers it necessary from a safety/tolerability point for an upcoming dose group/cohort. c. The follow-up period for a dose cohort may be prolonged if evolving PK data require a longer follow-up period.	I. A maximum extended in-house or follow-up period cannot be defined as the extension will be as long as necessary to ensure the safety of the individual participant(s). II. The maximum extended in-house or follow-up period for study cohorts will be based on evolving safety, tolerability and PK data and will not usually exceed 10 x t½ of the IMP following the last dose. [III. Extension of in-house or follow-up period does not constitute an SAE, unless a subject is hospitalised as patient of the National Health Service or the AE meets other SAE criteria.
	11. Additional safety blood and/or urine samples/variables may be taken or analysed if: a. It is considered clinically necessary by the PI or delegate for individuals on a case-by-case basis. b. The SRC considers it necessary from a safety/tolerability point for an upcoming dose cohort.	I. For individuals, a maximum number of safety blood samples will be determined on a case-by-case basis and cannot be pre-defined as investigations will be performed as necessary to ensure the safety of the individual participants. II. For dose cohorts, study specific maximum blood volumes will not be exceeded (see section 12.7).
	12. Timing of PK and/or immunogenicity samples may be adjusted in accordance with evolving data and dosing schedule. 13. Additional or less PK and/or immunogenicity samples may be taken in accordance with evolving data and dosing schedule.	I. Minimum: sufficient PK samples to establish full protocol specific serum PK profile. Sufficient immunogenicity samples to enable evaluation of de novo antibody development. II. Study specific maximum blood volume will not be exceeded (see section 12.7).
	14. Timing of safety assessments including but not limited to laboratory safety samples, vital	I. Alterations in timing of the safety assessments need to be a reflection of the established PK, safety and

Adaptive Study Design Areas	Features	Limits
	signs and ECGs may be adjusted in accordance with evolving data and dosing schedule. 15. Additional safety assessments including but not limited to laboratory safety samples, vital signs and ECGs may be taken in accordance with evolving data and dosing regimens.	tolerability profile up to the decision making time-point. II. Alterations need to be made in the spirit of the current CSP (i.e. focus on the capture of essential and useful data) and not affect the risk profile of the study.
	16. Specialist referrals (e.g. to a cardiologist) may be made (and may include all relevant assessments and investigations) if it is considered clinically necessary by the PI or delegate or Sponsor or SRC for individuals on a case-by-case basis.	I. A maximum for individuals will be determined on a case-by-case basis and cannot be pre-defined as investigations will be performed as necessary to ensure the safety of the individual participants.
	17. Except for those subjects that have been randomised, screening assessments, including Holter ECG recordings performed at Richmond Pharmacology Ltd on volunteers screened for another study can be used for this study to avoid unnecessary tests.	I. The assessments must meet protocol criteria (e.g. the method to be used) II. The assessments must be performed within the protocol defined screening window III. The Holter ECG recordings are valid for a period of three months.
AEs	18. Allow for the study to continue under the originally approved CSP and IMPD in case of new pre-clinical or clinical findings.	I. Applicable only for findings which do not affect the risk profile or objectives of the study.

Study Plan

Single doses of MOTREM (LR12) or matching placebo (Part B) are planned to be administered following a sequential group design in 26 healthy young male subjects aged from 18 to 45 years: Part A (Groups 1 and 2 of 1 subject each) followed by Part B (Groups 3 to 8 of 4 subjects each). For Part A (Groups 1 and 2), one subject each will receive MOTREM. For Part B (Groups 3 to 8) 3 subjects will receive MOTREM and 1 subject will receive placebo (3:1 ratio). Dose escalation to the following scheduled dose will only occur after satisfactory review of all safety and tolerability data by the Safety Review Committee in accordance with Table 1, protocol sections 8.2 Rules for dose escalation/progression and 8.3 Toxicity rules.

Subjects will be screened within 14 days and may be performed over multiple days prior to entering the study on Day -1. Each subject will receive verbal and written information followed by signing of the Informed Consent Form (ICF) prior to any screening procedures taking place. Subjects will be admitted on Day -1 and on Day 1 of the study each subject will receive MOTREM (LR12). All the subjects from Part A (Groups 1 and 2) and Part B (groups 3 to 8) will be discharged on Day 2 after 24h post-dose (start of infusion). They will attend the unit for a follow-up visit on Day 8±1. The End of Study visit will take place on Day 28±2. All the assessments performed during the study are detailed in the Study Plan (Table 2 and Table 3). Study design features as well as number of subjects may be adapted according to Table 1.

The end of study is defined as the last subject, last visit (LSLV).

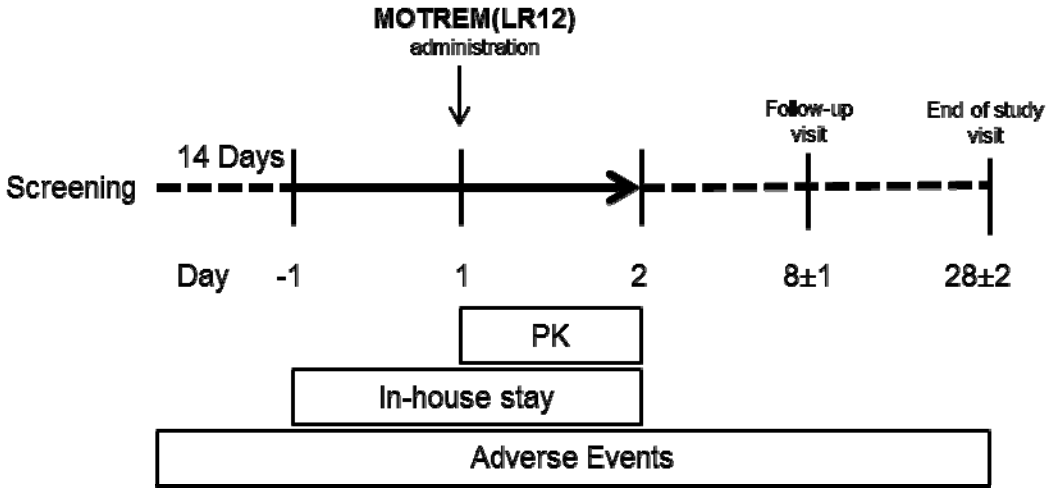


Figure 1: Study Flow Chart.

Table 2. Study Plan – Part A (Groups 1 and 2).

Groups 1 and 2	Screening		Assessment Period										FU Visit	EOS Visit
	D-14 to D-2	D-1	D1									D2	D8±1	D28±2
			Predose	H0	H1	H2	H3	H4	H5	H6	H7	H8	H24		
SCREENING PROCEDURES															
Signature of the informed consent	X														
Medical history	X	X													
Prior medications	X	X													
Physical examination	X	X(1)											X(1)	X(1)	X(1)
Viral Serology	X														
Alcohol breath test & Urine Drug Screen	X	X													
Inclusion / exclusion criteria	X	X													
Randomisation				X											
24h Holter	X														
Hospitalisation															
Study treatment schedule				T0' to T15'											
Meals(2)		X						X							
SAFETY ASSESSMENTS (3)															
Vital signs(4) (including BMI assessment at screening)	X	X	X	T0', T10', T20, T30, T40, T50'	X	X	X	X	X	X	X	X	X	X	X
ECG	X	X	X	T15'	X	X							X		
Telemetry (5)			←									→			
Haematology	X	X		T15'				X					X		
Coagulation	X	X		T15'				X					X		
Serum chemistry	X	X		T15'				X					X		
Urinalysis	X	X											X		
Infusion site assessment			X	T15' (6)	X			X					X		
Anti-LR12 antibody screening(7)			X											X	X
Pharmacokinetics			X	T15'	X										
Adverse Events	←														→
Concomitant medication	←														→

(1) Brief physical examination.
(2) Standard meals will be served at standard times. Meal at dismissal will be optional.
(3) Time of procedures is relative to the start of infusion.
(4) Tympanic temperature will be collected at predose and at H8 only. Vital signs at H0 will be measured only in supine position.
(5) 12-Lead telemetry will be recorded from pre-dose to 10 h post-dose.
(6) The check of the local tolerability at H0 should be performed just after the loading infusion
(7) Should any subject develop ADA against LR12, they will be followed up for at least 3 months or until the antibody response is no longer detected.
.

Table 3. Study Plan – Part B (Groups 3 to 8).

Groups 3 to 8	Screening		Assessment Period											FU Visit	EOS Visit
			D1										D2		
	D-14 to D-2	D-1	Predose	H0	H1	H2	H3	H4	H5	H6	H7	H8	H10	H24	D8±1	D28±2
SCREENING PROCEDURES																
Signature of the informed consent	X															
Medical history	X	X														
Prior medications	X	X														
Physical examination	X	X(1)												X(1)	X(1)	X(1)
Viral Serology	X															
Alcohol breath test & Urine Drug Screen	X	X														
Inclusion / exclusion criteria	X	X														
Randomisation				X												
24h Holter	X															
Hospitalisation																
Study treatment schedule				i.v. loading dose T0 to T15'	i.v. maintenance dose over 7 hours and 45 minutes											
Meals(2)		X	X											X		
SAFETY ASSESSMENTS (3)																
Vital signs(4) (including BMI assessment at screening)	X	X	X	T0', T10', T20, T30, T40, T50'	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X	X	X	T15'	X							X	X	X		
Telemetry (5)			←										→			
Haematology	X	X		T15'				X						X		
Coagulation	X	X		T15'				X						X		
Serum chemistry	X	X		T15'				X						X		
Urinalysis	X	X												X		
Infusion site assessment			X	T15' (6)	X	X		X		X		X		X		
Anti-LR12 antibody screening(8)			X												X	X
Pharmacokinetics(7)			X	T5', T15', T18', T30', T45'	X	X		X		X		T-15, T2', T4', T7', T15', T30	X			
Adverse Events	←														→	
Concomitant medication	←														→	

(1) Brief physical examination.
(2) Standard meals will be served at standard times. Meal at dismissal will be optional.
(3) Time of procedures is relative to the start of infusion.
(4) Tympanic temperature will be collected at pre-dose and at H8 only. Vital signs at H0 and H8 will be measured only in supine position.
(5) 12-Lead telemetry will be recorded from pre-dose to 10 h post-dose.
(6) The check of the local tolerability at H0 should be performed just after the loading infusion.
(7) PK sampling performed at the end of the 8 hours i.v. infusion will be as follows: 15 min before H8 (T-15'), then during 30 min after the end of the infusion as specified in the table. H0 timings refer to start of infusion.

(8) Should any subject develop ADA against LR12, they will be followed up for at least 3 months or until the antibody response is no longer detected.

8.2 Rules for Dose Escalation/Progression

A safety review committee (SRC) will review and assess at least the minimum required data from the previous group(s)/cohort(s) to make decisions on the dose(s) for the next dose levels/dosing regimen. The SRC will assess if any of the group or individual toxicity criteria are met and if the concerned AEs have a causal relationship with the IMP. If so, the SRC will take action in accordance with the rules stipulated in section 8.3.

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

8.2.1 Safety Review Committee

The SRC will consist of, as a minimum:

- Principal Investigator (RPL) or delegate
- INOTREM SA Medical Officer or delegate

Further internal or external experts such as a pharmacokineticist and/or a statistician, may be consulted by the SRC as necessary. Any additional information, if required will be included in the study operations manual (SOM).

8.2.2 Data Requirements

After each cohort the SRC will assess the minimum safety, tolerability and PK data required prior to dose escalation/progression (refer to dose escalation/progression section 8.2.4. Prior to each SRC meeting, an interim safety report will be prepared for that group/cohort presenting the relevant safety and tolerability data. These will be signed by the PI and/or delegate. PK data will be provided separately by the analytical laboratory. As the initial data review will be blinded, there will be no link between the safety data and the PK data.

The following data will be required:

Safety:

- AEs
- Vital sign variables (temperature, blood pressure, heart rate)
- ECGs variables (12-lead ECG, telemetry and Holter)
- Clinical laboratory variables (haematology, coagulation, biochemistry, urinalysis)

PK

For availability of PK data, refer to section 8.2.4.

Additional data that may available at the time of report writing:

- Other relevant clinical tests conducted on a case-by-case basis

8.2.3 SRC Meeting

The SRC will determine dose escalations/progression according to the Clinical Study Protocol (CSP), anticipated doses, adaptive features and group toxicity rules. The decision will be signed by one of the Sponsor's representatives and by the PI or delegate. For logistical reasons, the signature of the Sponsor or Investigator may be communicated via email.

Initially the data will be reviewed blinded, but if the SRC consider it necessary due to a safety concern, either individual subjects or the entire cohort may be unblinded to enable their decision-making. Before breaking the code, the potential decisions and actions should be determined and documented.

The decision of the SRC on the next dose will be taken in consensus between the members of the SRC. If consensus cannot be reached, then the most cautious approach will proceed. The decisions and decision-making of the SRC on the next dose level will be documented and provided to the PI and Pharmacist prior to the next scheduled dosing day.

8.2.4 Dose Escalation/Progression

Dose escalation /progression is defined as either of the following:

1. Escalation to a higher exposure dosing regimen within Part A
2. Progression from Part A to Part B
3. Escalation to a higher exposure dosing regimen within Part B

Minimum data requirements for dose escalation/progression are:

1. **Escalation to a higher exposure dosing regimen between Part A (Groups 1 and 2 and optional groups)**
   A minimum of 24 hours post-dose (start of infusion) safety and tolerability data from one subject of the cohort with the next lower mean exposure level will be required.
2. **Progression from Part A to Part B**
   A minimum of 24 hours post-dose (start of infusion) safety and tolerability data from one subject on Part A's 10mg dose level will be required.
3. **Escalation to a higher exposure dosing regimen between Part B (Groups 3 to 8 and optional groups)**
   A minimum of 24 h post-last dose (start of infusion) safety, tolerability and PK data from a minimum of three subjects who have received the active compound from a previous cohort that was on the next lower dosing regimen (and hence, next lower exposure (mean and individual Cmax) levels of loading dose and mean and individual Cmax and Css inf of maintenance doses) will be required.

8.3 Toxicity Rules

Group toxicity rules

For the purpose of this CSP, toxicity means clinically significant drug related adverse reaction(s).

For the purpose of this CSP the term 'dose escalation' means progression to a consecutive dose/dosing regimen or escalation to a dose/dosing regimen with an anticipated higher exposure in line with the dose progression/escalation rules and minimum data requirements.

For the purpose of this CSP the term 'suspension' means that no further IMP will be administered at the dose level/dosing regimen concerned and that further dose escalation/progression will be suspended. If a dose level/dosing regimen is suspended, an ad hoc SRC meeting will be held. Any resumption at the same or a higher exposure dose level/dosing regimen will require a substantial amendment which has been approved by the Competent Authority and the REC.

The group toxicity rules are described in Table 4.

Table 4. Group Toxicity Rules.

CTCAE Grade	Severity/ Seriousness	Reversibility	Number of Subjects Affected	Action	Effect on Dose Progression/Escalation
I	Mild	N/A	N/A	Next dose determined by SRC	N/A
II	Moderate	Showing signs of reversibility; i.e. event which shows signs of improvement in the judgment of investigator	≤2 subjects in different SOC		
			≤2 subjects in same SOC OR 3 subjects in different SOC*	Dose level may continue OR be extended AND Dose escalation on hold until results of continuation or extension are available	Following continuation or extension, dose escalation may proceed as per clinical study protocol
			≥3 subjects in same SOC OR ≥4 subjects in different SOC*	Dose level suspended	A lower (intermediate) dose level may be administered in the next cohort AND Dose continuation, extension, or escalation requires substantial amendment
		Showing no signs of reversibility	≥2 subjects*		
III	Severe, not serious	Showing signs of reversibility; i.e. event which shows signs of improvement in the judgment of investigator	1 subject*	Dose level may continue OR be extended AND Dose escalation on hold until results of continuation or extension are available	Following continuation or expansion, dose escalation may proceed as per the clinical study protocol
			≥2 subjects*	Dose level suspended	A lower (intermediate) dose level may be administered in the next cohort AND Dose continuation, extension, or escalation requires substantial amendment
		Showing no signs of reversibility	≥1 subject		
	Severe, serious	N/A			
IV	Life-threatening	N/A	≥1 subject	Study suspended	Study continuation requires substantial amendment
V	Fatal				

Abbreviations: AE=adverse event; N/A=not applicable; SOC=System Organ Class; SRC=Safety Review Committee

* Within 2 weeks from each dose

Individual stopping criteria

Individual stopping criteria are described in Table 5.

Table 5. Individual Toxicity Rules.

Individual toxicity rules		
Grade	Severity/Seriousness	Action
I	Mild	No action required
II	Moderate	IMP administration may be continued, amended, temporarily suspended or discontinued in accordance with Investigator's clinical judgement and relevant algorithms for the treatment of toxicities
III	Severe, not serious	IMP administration will be discontinued for the subject
	Severe, serious	IMP administration will be discontinued for the subject
IV	Life-threatening	IMP administration will be discontinued for the subject
V	Fatal	Not Applicable

Standard toxicity grading according to the National Cancer Institute Common Terminology Criteria (NCI CTC) for AEs (NCI CTCAE, version 4.0) will be used to grade the AEs for the purpose of applying the toxicity rules. This is owing to the fact that these are the only standardised set of comprehensive criteria available and have proven useful in healthy volunteer and patient Phase 1 studies. Local laboratory normal values will be applied. Abnormal laboratory and other tests and measurements will be repeated whenever feasible and or appropriate, prior to grading in order to ensure consistency and to exclude technical errors. Diurnal variations in laboratory variables and other measurements as well as baseline status and conditions will be taken into account when assessing whether abnormalities constitute a drug related AE and when grading, if applicable.

The CTCAE displays AE/toxicity Grades I through V with detailed clinical descriptions of severity for individual AEs based on a general guideline. The general grade definitions are described as follows:

Grade I: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade II: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)*.

Grade III: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL**.

Grade IV: Life-threatening consequences; urgent intervention indicated.

Grade V: Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The NCI CTCAE criteria and their interpretation are consistent with the standard intensity grading for AEs during clinical studies: Grade I: mild, Grade II: moderate, Grade III: severe

or medically significant but not immediately life-threatening, may constitute Serious Adverse events (SAE)/Suspected Unexpected Serious Adverse Reaction (SUSAR). Grades IV and V constitute SAE/SUSAR.

Non-clinical data as well as potential class effects have identified the risks outlined in sections 6.4.2.1, 6.4.2.3 and 6.4.2.4 (allergic reactions, infusion reactions and anaphylaxis; product specific antibody development).

The grading of the NCI CTCAE criteria related to toxicities and potential AEs (including study related sections on: 'infusion related reaction', 'injection site reaction', 'allergic reaction' 'anaphylaxis', 'Immune system disorders' – specifically 'autoimmune disorder') is considered suitable for this particular IMP, study design and the study populations in conjunction with the CSP specific toxicity and dose progression/escalation rules. No further qualifications are required.

8.4 Rationale for Study Design, Doses and Control Groups

This study is the first time that MOTREM will be given to healthy young subjects.

A standard single dose escalation design is used for this study to evaluate the safety, tolerability and PK of the investigational product in healthy subjects. The study is randomised and double blind (Part B only) to minimise bias and includes placebo to facilitate identification of effects related to administration of drug rather than the study procedures or situation.

For the first two dose levels (Part A) there will be no placebo and only one subject will be dosed, as these dose levels are well below the expected therapeutic dose range and expected to be below the limit of quantification in human blood and therefore not considered informative (9).

8.4.1 Justification of Safe Starting Dose

Regulatory References

Toxicity studies were performed at INOTREM in accordance with ICH guidance documents S6/R1 and M3 (R2) as well as to EMA's guidance on repeated dose toxicity (EMEA/CHMP/SWP/488313/2007) and FDA guidance "Immunogenicity Assessment for Therapeutic Protein Products".

The safe starting dose of LR12 in the first-in-human study MOT-C-104 was estimated according to the principles laid out in the guidance documents "Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. FDA/CDER, July 2005" and the "Guideline on Strategies to Identify and Mitigate Risks for First-in Human Clinical Trials with Investigational Medicinal Products CHMP/SWP/28367/07".

Relevant Species Selection

Since (i) LR12 sequence displays an identical amino acid sequence for both human and cynomolgus monkey TLT-1 protein and (ii) LR12 is pharmacologically active in this species, the cynomolgus monkey was selected as the relevant animal species to perform toxicity studies. In addition, the pharmacokinetic behaviour of LR12 is expected to be similar in cynomolgus monkeys and humans. The corresponding LR12 sequence of rodents differs from human and cynomolgus LR12 by two amino acids.

No Observed Adverse Effect Level (NOAEL) Determination

For establishing the safe starting dose, only the 14-day GLP toxicity study in cynomolgus monkeys with the clinical formulation is considered (MOT-PT-10). In this study, monkeys were exposed to an initial high loading dose for 15 minutes followed by a maintenance dose administered by continuous IV infusion for 14 days. The NOAEL was then set as the highest dose administered in that study (140 mg/kg/day with a loading dose of 20 mg/kg/15 minutes, see Table 6 and Table 7).

Human Equivalent Dose (HED) Calculation

According to the "Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. FDA/CDER, July 2005", normalisation to body surface area is an appropriate method for extrapolating doses between species (hereafter referred to as "HED BS"). However, certain exceptions are made. It is considered that scaling based on body weight (i.e. setting the HED (mg/kg) = NOAEL (mg/kg) and referred to in this document as "HED BW") may be appropriate for therapeutics that will have little distribution outside the intra-vascular compartment. There is some evidence that LR12 mainly remains in the i.v. compartment after administration. However, distribution of LR12 is not yet fully characterised.

On the other hand, the clearance of LR12 is very fast in monkeys and it is expected to be similar in humans. Since LR12 is planned to be administered continuously by i.v. infusion to maintain steady state concentrations, as it has been done in efficacy pharmacology models, it is necessary to consider exposure time to LR12 at a given plasma concentration/infusion rate in order to determine appropriate safety margins.

For the above mentioned reasons, both approaches HED BS and HED BW will be taken into consideration as well as rate of infusion and time of exposure in order to calculate the safety margin for this FIH study.

8.4.1.1 Determination of Safe Starting Dose

The safety factor recommended by regulatory guidance documents is 10. However, considering that LR12 is a novel therapeutic agent, we have increased greatly this safety margin.

The first dose planned to be administered to humans is 1 mg as a "loading" dose infused i.v. for 15 minutes. This will be equivalent to a rate of infusion of 0.057 mg/kg/h and to 0.014 mg/kg dose for an individual of 70 kg.

The reference NOAEL and its conversion to HED BS is shown in Table 6. The reference "loading dose" and its conversion to HED BS for the group of animals that have received the highest loading dose in the toxicology study MOT-PT-10 is presented in Table 7.

Table 6. NOAEL and HED BS.

Study	Exposure Time[1]	NOAEL mg/kg/day	NOAEL mg/kg/hour	HED BS[2] mg/kg/day	HED BS[1] mgkg/hour
MOT-PT-10	24 h	140	5.83	45.16	1.88

1: Refers to a period of 24h of a 14-day repeated toxicity study used here as the reference exposure period

2: HED calculated according to FDA Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (2005) body surface conversion table. Animal dose is divided by a factor of 3.1 for cynomolgus monkeys.

Table 7. Highest Loading Dose and HED BS.

Study	Exposure time	NOAEL mg/kg/15 min	NOAEL mg/kg/hour	HED BS[1] mg/kg/15 min	HED BS[1] mg/kg/hour
MOT-PT-10	15 min	20	80	6.45	25.81

1: HED calculated according to FDA Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (2005) body surface conversion table. Animal dose is divided by a factor of 3.1 for cynomolgus monkeys.

According to this, the starting dose rate in mg/kg/h will be 33 times lower than the NOAEL HED BS (1.88 versus 0.057) and 102 times lower than the NOAEL HED BW (5.83 versus 0.057). In terms of total exposure, knowing that the reference taken in toxicology studies is of 24 hours and that total exposure time for human starting dose will be 15 minutes, the total exposure in a one-day period in mg/kg will be 3226 times lower on the basis of HED BS (45.16 versus 0.014) and 10000 times lower on the basis of HED BW (140 versus 0.014).

If the highest loading dose given during the toxicology study is considered, the starting dose rate in mg/kg/h will be 453 times lower by HED BS conversion (25.81 versus 0.057) and a 1403 times lower by HED BW conversion (80 versus 0.057). In terms of total exposure, the total exposure in a 15-minute period in mg/kg will be 461 times lower on the basis of HED BS (6.45 versus 0.014) and 1429 times lower on the basis of HED BW (20 versus 0.014).

These margins are considered to be sufficiently wide to assure safety of healthy volunteers who will receive LR12 for the first time.

8.4.1.2 Justification of Dose Escalation Steps

The planned dose escalation scheme of the FIH study MOT-C-104 is summarised in Table 8:

Table 8. Planned Dose Escalation Scheme.

Group	Loading dose			Maintenance dose		
	(mg/kg) 15 min	Rate (mg/kg/h)	Total (mg)*	Rate (mg/kg/h)	Total 7h45 (mg/kg)	Total 7h45 (mg)*
1	0.014	0.057	1	-	-	-
2	0.140	0.570	10	-	-	-
3	0.500	2.000	35	0.03	0.23	16.3
4	1.000	4.000	70	0.10	0.78	54.3
5	2.000	8.000	140	0.30	2.33	162.8
6	5.000	20.000	350	1.00	7.75	542.5
7	5.000	20.000	350	3.00	23.25	1,627.5
8	5.000	20.000	350	9.00	69.75	4,882.5

*Assuming a body weight of 70kg

The second dose planned to be administered to humans is 10 mg as a “loading” dose infused i.v. for 15 minutes. This will be equivalent to a rate of infusion of 0.57 mg/kg/h and to 0.14 mg/kg dose for an individual of 70 kg.

According to this, the second cohort dose rate in mg/kg/h will be 3.3 times lower than the NOAEL HED BS (1.88 versus 0.57) and 10 times lower than the NOAEL HED BW (5.83 versus 0.57). In terms of total exposure, knowing that the reference taken in toxicology studies is of 24 hours and that total exposure time for this cohort will be 15 minutes, the total exposure in a one-day period in mg/kg will be 323 times lower on the basis of HED BS (45.16 versus 0.14) and 1000 times lower on the basis of HED BW (140 versus 0.14).

If the highest loading dose given during the toxicology study is considered, the second cohort dose in mg/kg/h will receive a 45 times lower dose by HED BS conversion (25.81 versus 0.57) and a 140 times lower dose according to HED BW (80 versus 0.57). The total exposure in a 15 minutes period in mg/kg will be 46 times lower on the basis of HED BS (6.45 versus 0.14) and 143 times lower on the basis of HED BW (20 versus 0.14).

From cohorts 3 to 6, the loading dose will be increased incrementally by a factor 2 (or 2.50).

The first maintenance dose rate will be introduced in cohort 3 and is of 16.3 mg at an infusion rate of 0.03 mg/kg/h for a total exposure time of 7h45. This corresponds to 0.23 mg/kg dose for an individual of 70 kg.

According to this, the third dose rate for the maintenance dose in mg/kg/h will be 63 times lower than the NOAEL HED BS (1.88 versus 0.03) and 194 times lower than the NOAEL HED BW (5.83 versus 0.03). In terms of total exposure, knowing that the reference taken in toxicology studies is of 24 hours and that total exposure time for the maintenance dose in humans will be of 7 hours 45, the total exposure in a one day period in mg/kg will be 196 times lower on the basis of HED BS (45.16 versus 0.23) and 609 times lower on the basis of HED BW (140 versus 0.23).

From cohorts 3 to 8, the maintenance dose will be increased incrementally by a factor 3.

For information, in preclinical efficacy pharmacology experiments in LPS-challenged cynomolgus monkeys, LR12 at a loading dose of 10 mg/kg/h for a period of 30 minutes and a maintenance dose of 1 mg/kg/h for 7.5 hours was pharmacologically active. In this model, this dose was able to avoid hypotension and diminish the increase of several pro-inflammatory cytokines by 20-50% in comparison with untreated animals. This dose would approximately correspond to the dose that will be administered to the cohort 5 of the present study if we consider the HED BS and to the dose that will be administered to the cohort 6 if we consider the HED BW. However, an LR12-induced pharmacological effect is not expected in healthy volunteers since their innate immune system would not be activated.

Justification of highest dose level

The anticipated highest dose regimen that will be tested (cohort 8) is a loading dose of 5 mg/kg administered during 15 minutes (20 mg/kg/h) followed by a maintenance dose of 69.75 mg/kg, administered during a period of 7h45 (9 mg/kg/h).

The highest loading dose will be introduced in cohort 6 (Table 3). This dose in mg/kg/h will be 1.3 times lower by HED BS conversion (25.81 versus 20) and 4 times lower if HED BW is used (80 versus 20). For this cohort, the total exposure in a 15 minutes period in mg/kg will be 1.3 times lower on the basis of HED BS (6.45 versus 5) and 4 times lower on the basis of HED BW (20 versus 5).

In a pilot toxicity study (MOT-PT-01), two monkeys received 18.75 mg/kg/h during a period of 24h, meaning 450 mg/kg (Twice higher rate than the maintenance dose planned in cohort 8 if HED BW is considered). In this study no drug-related adverse event was observed. In terms of total dose in a period of one day, cohort 8 individuals will receive 69.75 mg/kg. In comparison to this pilot study, the total dose that will be administered to cohort 8 is around twice lower if HED BS is used (145.2 versus 69.75) and 6 times lower if HED BW is used (450 versus 69.75). In addition, in a GLP cardiovascular function safety pharmacology study (MOT-PT-02), four monkeys received 18.4 mg/kg/h during 24 hours (total dose of 442 mg/kg) and did not show any drug-related adverse event. Therefore, the highest dose is expected to be safe.

Of importance, in order to further minimise the risk to study subjects in study MOT-C-104, the safety of subjects will be monitored closely and escalation to higher dose levels will be allowed only after careful review by the Safety Review Committee of all clinical and laboratory analysis performed in volunteers (see sections 8.2 and 8.3).

8.4.2 Choice of Subjects for Study

Male subjects, aged between 18 and 45 years considered healthy for their age are planned to be included in Part A (Groups 1 and 2) and B (Groups 3 to 8). The selection criteria are defined such that subjects selected for participation in the study are known to be free from any significant illness which potentially could confound the study results. Healthy subjects are also unlikely to require concomitant treatments which could interfere with the study drug. Female volunteers are not included in this study because investigations on teratogenicity have not been performed.

8.4.3 Route and Rate of Administration

MOTREM will be administered as an i.v. infusion. In this study, dose levels were calculated from pre-clinical data. Dose escalation will proceed with accordance with Table 1 of adaptive features and will not exceed the mean maximum exposure limits.

8.4.4 Precautions to be Applied for Dosing Between Subjects within a Cohort

For each cohort, treatment of subjects will begin on Day 1.

Dose groups 1 and 2 will receive a single i.v. dose of MOTREM. Then, dose groups 3 to 8 will receive a 15 minute i.v. loading dose of MOTREM followed by 7.45 hours of continued i.v. infusion or matching placebo.

In order to avoid simultaneous exposure of all subjects on the same day to a given dose, each cohort will be split in two groups: a mandatory sentinel dosing strategy of dosing one subject on IMP on the first day will be used for each cohort. If safety and tolerability is acceptable the remaining subjects of each cohort will be dosed in group sizes of no more than three with a minimum interval of 24 hours between the start of dosing in the first subject on the previous day and the start of dosing on the next day. In addition, during a dosing day, there will be a minimum interval of 60 minutes between the start of (maintenance) dosing in a subject and the start of dosing in the next subject. Vital signs data recorded in each subject at T+50 min will be reviewed and AE checked before dosing the next subject. In case of significant abnormalities in these data, the next subject may not be dosed, or dosing may be delayed, according to the investigator's judgment.

The Investigator will document the decision to proceed from mandatory sentinel dosing to dosing of the remainder of a cohort in an e-mail to the Sponsor. The e-mail does not require Sponsor's response, unless there is disagreement with the Investigator's decision.

8.4.5 Precautions to be Applied for Dosing Between Different Cohorts

Please refer to section 8.2.

8.4.6 Monitoring and Communication of Adverse Events / Reactions

Adverse events (AEs) will be continuously monitored throughout the study from day of consent until the last follow up assessment. Each AE reported will be assessed by a trained Research Physician who will ensure that the event is dealt with as appropriate based on clinical need, study protocol, study operations manual and Richmond Pharmacology standard operating procedures (SOPs). Following discharge from the unit the subjects will be encouraged to phone the investigator immediately in case they experience any AEs and/or take any concomitant medication. AEs will be documented in the subjects' Case Report Forms (CRFs) and reviewed regularly by the Research Physicians and the Investigator.

If any information relating to the study drug in this study becomes available after the submission of a final protocol to the Competent Authority which may impact on the conduct of the study, including but not limited to the risk and benefit evaluations underpinning approvals and volunteer's consent, INOTREM SA shall notify RPL in writing as soon as practically possible and the parties will agree, in writing, what steps need to be taken if any.

8.4.7 Investigator Site Facilities and Personnel

This study will be conducted in a specialised early phase CPU within an acute hospital setting with Critical Care facilities, thus ensuring direct access to equipment and staff for resuscitating and stabilising subjects in acute medical conditions and emergencies. The study is conducted by an experienced PI and well trained medical, nursing and technical staff with ample experience in the conduct of early phase clinical trials.

The study is designed to closely monitor, treat and communicate potential expected adverse reactions as well as potential unexpected adverse events.

9 SELECTION AND WITHDRAWAL OF SUBJECTS

9.1 Number and Source of Subjects

26 subjects are planned (i.e. 2 first groups of one healthy male subject each and 6 groups of 4 healthy male subjects). The number of subjects in a dose cohort can be extended to gather further information on a dosing regimen, withdrawn subjects can be replaced at the discretion of the sponsor and investigator, if not withdrawn for safety reasons and replacement subjects may be enrolled in an ongoing cohort, or dosed together as a group or dosed separately. The total number of subjects will not exceed 72 subjects (Table 9).

Table 9. Number of subjects

	Part A	Part B	Total
Planned cohorts	2 (2x1=2)	6(6x4=24)	26
Optional Cohorts	2 (2x1=2)	2(2x4=8)	10
Extended cohorts	2 (2x1=2) 2 (2x1=2)	6(6x4=24) 2(2x4=8)	36
Total	8	64	72

Optional groups/cohorts may be included to explore additional dose levels and/or dosing regimen. Please refer to Table 1.

Inclusion and exclusion criteria for enrolling subjects in this trial are described in the following sections.

9.2 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for enrolment in this study:

1. Male subjects aged 18-45 years old (both ages included),
2. Subjects must be in good health as determined by their medical history, physical examination, ECG, vital signs, and laboratory tests,
3. Subjects with a body mass index within the range 18-30 kg/m^2 (both inclusive),
4. Subjects must agree with methods of contraception as outlined in Section 9.4,

5. Subjects must have signed an informed consent form indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study and comply with the study procedures and restrictions,

9.3 Exclusion criteria

Subjects will be excluded from enrolment in this study if they meet any of the following criteria:

1. Subjects with any medical history, conditions or risks, which, in the opinion of the investigator, may interfere with the subject's full participation in the study, or compliance with the protocol, or pose any additional risk for the subject or confounds the assessment of the subject or outcome of the study.
2. History of significant respiratory, renal, endocrinologic, hepatic, gastrointestinal, haematological, lymphatic, neurological, cardiovascular, psychiatric, musculoskeletal, genitourinary, immunological, dermatological or connective tissue disease or diseases,
3. History of malignancy,
4. History of relevant drug or other significant allergy,
5. Likely to need any treatment (including dental care) during the study period,
6. Significant infection or known inflammatory process at screening or Day -1,
7. Recent vaccination in the previous 2 weeks (from screening),
8. Donation or loss of more than 400 mL of blood within 90 days prior to the screening,
9. Use of any prescribed or over-the-counter medication within 14 days prior to first dosing (not including paracetamol in the range of 1g/day) or within 6 times the elimination half-life of the medication prior to first dosing (whichever is longest),
10. History or clinical evidence of alcohol or substance abuse. Alcohol abuse is defined as regular weekly intake of more than 21 units for males.
11. Confirmed positive results from urine drug screen (methamphetamine, opiates, cocaine, cannabis) or from the alcohol breath test at screening and on admission.
12. Current smokers (within 3 months prior to screening) and those who have a positive cotinine test,
13. Subjects who do not have suitable veins for multiple venipunctures/cannulation as assessed by the investigator at screening,
14. Supine blood pressure (BP) greater than 140/90 mmHg (systolic/diastolic) or less than 90/60 mmHg confirmed by at least 2 repeated measurements at screening and D-1,
15. Subjects who have clinically relevant ECG abnormalities (e.g. QTcB > 450 ms or notable sinus bradycardia with mean HR<40 bpm) confirmed by a repeat ECG at screening and D-1,
16. Family history of congenital long QT syndrome or known congenital arrhythmia,
17. Liver enzymes (ALAT, ASAT, ALP) exceeding the upper limit of normal range or 1.5 times the upper limit on D-1,

18. Renal impairment or calculated glomerular filtration rate (according to Modification of Diet in Renal Disease (MDRD)) < 80 mL/min/1.73 m2 at screening,
19. Positive results for serology test (HIV-1 and 2, Hepatitis B surface antigen (HBsAg), hepatitis C antibody (anti-HCV)),
20. No legal capacity or limited legal capacity or unable to give an informed consent.
21. Subjects with pregnant partners

9.4 Subject Restrictions

Subjects will have to comply with the following restrictions during the study:

1. Whenever subjects are confined in the ward, only the drinks and meals provided by the trial personnel will be allowed.
2. Standard meals will be provided at the standard unit times as stated in the study plan, and meals should be completed each time.
3. Subjects will be required to fast for a period of at least 8 hours before study drug administration.
4. Intake of caffeine will not be allowed 12 hours before screening and then from 12 hours prior to study drug administration until discharge. During the subjects' outpatient periods, subjects should also limit their caffeine intake to equivalent of 3 cups of coffee per day
5. Abstain from consumption of energy drinks containing taurine or glucuronolactone from the day of enrolment until the end of study visit.
6. Abstain from drinking alcohol from at least 48 hours before drug administration to end of study visit.
7. Abstain from consumption of nicotine during the study.
8. Not start any new physical training activities or increase the intensity of their usual physical training during the study.
9. Avoid any medication (including over the counter (OTC) products and herbals, vitamins and minerals) from 14 days before IMP administration (with the exception of paracetamol in the range of 1g/day) until the end of the hospitalisation in order to avoid interference with study assessments.
10. Abstain from blood and plasma donation during the study and up to three months after completion of the study.
11. Subjects must use acceptable methods of contraception if the male subject's partner could become pregnant from the time of the first administration of study medication until 3 months following administration of the last dose of study medication. One of the following acceptable methods of contraception must be utilised:
    - Surgical sterilisation (vasectomy with documentation of azoospermia) and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).

- The subject's female partner uses oral contraceptives (combination estrogen/progesterone pills), injectable progesterone, or subdermal implants and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
- The subject's female partner uses medically prescribed topically-applied transdermal contraceptive patch and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
- The subject's female partner has undergone documented tubal ligation (female steriliation). In addition, a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository) must be used.
- The subject's female partner has undergone documented placement of an IUD or IUS and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
- True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent subjects have to agree to use one of the above-mentioned contraceptive methods, if they start sexual relationships during the study and for up to 3 months after the last dose of study drug.
- Male subjects must use a condom with spermicidal foam/gel/film/cream/suppository if their female partner(s) is (are) pregnant or lactating from the time of the first administration of treatment or study medication until 3 months following administration of the last treatment or study medication administration.

9.5 Subject Inclusion and Randomisation

Subjects in this study will be assigned to a treatment regimen according to a randomisation schedule generated by a statistician using PROC Plan. Details regarding the unique screening and subject number will be included in the SOM.

For Part B (Groups 3 to 8), eligible subjects who meet the eligibility criteria will be randomly assigned on Day 1. Subjects will be randomly assigned in Part B (Groups 3 to 8) in a 3:1 ratio to either MOTREM (LR12) or Placebo.

9.6 Criteria for withdrawal

The Investigator or designee will withdraw a subject from the study if the subject:

- Is in major violation of the protocol
- Meets individual stopping criteria
- 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
- Requests to be withdrawn from the study (subject withdrawal of consent)
- Is found to be considerably non-compliant with the protocol-required dosing visits
- In the Investigator's opinion, is unable to continue study participation

- Is withdrawn from the study upon the request of Sponsor or the SRC, including if Sponsor terminates the study.

9.6.1 Handling of Withdrawals

In the event a subject withdraws or is withdrawn from the study, the Investigator will inform the Medical Monitor and the Sponsor immediately. The SRC will be notified. If there is a medical reason for withdrawal, the subject will remain under the supervision of the Investigator for protocol-specified safety follow up procedures.

Should any of the subjects be withdrawn from the study after being dosed, all the relevant assessments should be completed as per protocol.

Investigator and/or Sponsor may decide to perform additional assessments in accordance with Table 1 – Adaptive features 11, 12, 14, 16 and 17.

A subject who fails to return for evaluations will be contacted by the site in an attempt to have the subject comply with the protocol in accordance with the site SOPs.

When a subject withdraws from the study, the primary reason for discontinuation must be recorded in the appropriate section of the case report form (CRF).

10 STUDY AND CONCOMITANT TREATMENTS

10.1 Investigational Medicinal Products (IMPs)

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 10 shows the composition of MOTREM in vials and as reconstituted solution. IMP will be stored under appropriate conditions as described on the IMP vial label, in a reasonably secure +2 to +8°C refrigerator placed in a room of restricted access.

Table 10. Composition of MOTREM Drug Product and as Reconstituted Solution

		Drug Product[1] (per Vial)	Reconstituted Solution
Product	*Function*		Solution after reconstitution with 40 mL of 0.9% Sodium Chloride for Injection Ph Eur.
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 : Manufactured Product

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 the correct handling of the blinding. Placebo will be provided by the site. It will be a single batch dedicated for the purpose of the study (identical manufacturer and identical batch).

10.1.1 Doses and Treatment Regimen

Single doses of MOTREM (LR12) or matching placebo are planned to be administered i.v. as detailed in Table 11.

Table 11. Daily dose of IMP (MOTREM or matching placebo) for each dose group.

Dose group	i.v. loading dose T = 15'	Maintenance i.v. dose (mg/kg/h) T = 7h45'	Number of subjects
Group 1	1 mg	-	N = 1
		-	
Group 2	10 mg	-	N = 1
		-	
Group 3	0.5 mg/kg	0.03 mg/kg/h	N = 3
	Placebo	Placebo	N = 1
Group 4	1 mg/kg	0.1 mg/kg/h	N = 3
	Placebo	Placebo	N = 1
Group 5	2 mg/kg	0.3 mg/kg/h	N = 3
	Placebo	Placebo	N = 1
Group 6	5 mg/kg	1 mg/kg/h	N = 3
	Placebo	Placebo	N = 1
Group 7	5 mg/kg	3 mg/kg/h	N = 3
	Placebo	Placebo	N = 1
Group 8	5 mg/kg	9 mg/kg/h	N = 3
	Placebo	Placebo	N = 1

IMOTREM or placebo will be administered by a Research Physician and the details of dosing will be recorded in the CRF. The dosing will be verified by another member of the Investigator's staff.

The study drugs will be dispensed by the pharmacy staff at the clinical study site. The pharmacy staff 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 subject dose will be detailed in a Pharmacy Worksheet.

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

10.2 Labelling of IMPs

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 UK health authorities according to the submission requirements.

10.3 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 subject/patient in the study. Any reason for departure 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.

10.4 Blinding and Procedures for Unblinding the Study

10.4.1 Methods for Ensuring Blinding

The study will be conducted partly in a double-blind fashion (Part B only) whereby subjects and clinical study site staff are blinded to study drug/dose assignment.

The pharmacy staff preparing the investigational products will not be blinded to study drug assignment. During the study, the randomisation codes will be kept in the site's clinical trials pharmacy, accessible to the pharmacy personnel 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.

10.4.2 Methods for Unblinding the Study

In the event of an emergency, an envelope for each subject containing his study drug assignment will be available in the pharmacy at the clinical study site. Unblinding should only be considered for the safety of the subject. If unblinding is deemed necessary by the investigator, the investigator or designee can unblind the subject’s treatment allocation using the envelope available from the pharmacy. The investigator or designee must note the date, time and reason for unblinding and inform the sponsor of unblinding as soon as practicably possible.

10.4.3 Concomitant Medications/Permitted medications

Intake of any medication is prohibited from 14 days before IMP administration (with the exception of paracetamol in the range of 1g/day) until the end of the hospitalisation in order to avoid interference with study assessments.

During the study, medications other than IMP must only be taken exceptionally and with the consent of the investigator. The need for other medication may lead to subject’s withdrawal from the study. In any case, the investigator will inform the sponsor about the concurrent medication given.

Details of prior and concomitant medications should be recorded by the investigator on the CRF and source record.

Emergency equipment and drugs will be available within the clinical unit as per current standard procedures. In the unlikely event that they are required, their use will be documented.

11 STUDY PROCEDURES

11.1 Schedule of Study Procedures

The study assessments are described in the sections below and the timing of these assessments are detailed in the study plan (Table 2 and Table 3). The sequence of assessments at particular time-points will be described in the SOM.

12 STUDY METHODOLOGY

12.1.1 Meals

Standardised meals will be provided during the study period according to Study Plan (Table 2 and Table 3). Subjects will be fasted eight hours prior to dosing. The composition of the meals will be specified in the SOM.

12.1.2 Haematology and Biochemistry

Blood samples for determination of biochemistry, haematology and coagulation parameters will be taken at the times given in the Study Plan (Table 2 and Table 3). The date and time of collection will be recorded on the appropriate CRF pages. The analyses will be done using routine methods. Further details will be described in the SOM.

Laboratory values outside the reference limits, which are suspected to be of any clinical significance, will be repeated. Subjects in whom the suspected clinical significance is confirmed on repeated sampling will either not be included or, if already included, may be withdrawn from further participation in the study in accordance with the toxicity rules in section 8.3 and/or followed until normalisation or for as long as the Investigator considers necessary.

Laboratory parameters to be measured are presented in Table 12.

Table 12. Laboratory parameters.

Biochemistry	Haematology	Urinalysis	Serology	Urine Screen for Drugs of Abuse	Coagulation
Aspartate aminotransferase	Haemoglobin	Leukocytes	Hepatitis B surface antigen (HBsAG)	Benzodiazepines	Prothrombin time (INR)
Alanine aminotransferase	Haematocrit	Nitrite	Hepatitis B core antibody (anti-HBC IgG + IgM, if IgG positive)	Opiates	activated partial thromboplastin time (aPTT)
Alkaline phosphatase	Erythrocytes	Urobilinogen	Hepatitis C antibody (anti-HCV)	Amphetamines	Fibrinogen
Total Bilirubin	Mean corpuscular volume (MCV)	Protein	HIV I and II antibodies	Methadone	
Creatinine	Mean corpuscular haemoglobin concentration	pH		Cocaine	

Biochemistry	Haematology	Urinalysis	Serology	Urine Screen for Drugs of Abuse	Coagulation
	(MCHC)				
Urea	Mean cell haemoglobin (MCH)	Blood		Cannabinoids	
Glucose	Leucocytes	Urine microscopy		Barbiturates	
Sodium	Basophils	Ketones		Cotinine	
Potassium	Eosinophils	Bilirubin			
Chloride	Neutrophils	Glucose			
Calcium	Lymphocytes	Specific gravity			
Inorganic phosphate	Monocytes				
Total Protein	Platelet count				
CRP	Reticulocytes				
Albumin					
Albumin/globulin ratio					
Triglycerides					
Total Cholesterol					
eGFR*					

* eGFR is calculated by the Modification of Diet in Renal Disease (MDRD) equation:
$186 \times (Creat / 88.4)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$

12.1.3 Serology

Serology will be performed at Screening as detailed in the Study Plan (Table 2 and Table 3). At the screening visit all subjects will be tested for the parameters listed in Table 12. This is done for the safety of the study personnel and the result from the tests will not be entered into the study database. If a volunteer is found to be confirmed positive in any of these tests, they will be referred for further examination/treatment and will not be included in the study, with the exception of volunteers with a confirmed positive anti-HBc IgG and negative anti-HBc IgM and HBsAg, indicative of natural immunity due to a past infection without active chronic or acute infection

The serology tests will be analysed in the same blood sample used for biochemistry.

12.1.4 Urinalysis

Urine samples for determination of urinalysis parameters will be taken at the times given in the Study Plan (Table 2 and Table 3). If deemed necessary, based on a clinically significant positive test, microscopic examination of urine will be performed.

12.1.5 Drugs of Abuse

Urine will be tested for the drugs of abuse as described in the Study Plan (Table 2 and Table 3). If a subject fails the drug abuse screen, they will be excluded from the study. A repeat drug

screen can only be done where methodological reasons are believed to have led to a false positive. Borderline positive results, unless covered by the preceding condition, are to be considered as positive and the subject excluded from the study. If subjects are found to be positive due to medication e.g. flu/cold remedies, they may undergo a repeat drug screen if they are still within the screening window. The results from the tests will not be entered into the database.

12.1.6 Alcohol Breath Test

An alcohol breath test will be done using an alcometer as described in the Study Plan (Table 2 and Table 3). The results from this test will not be entered into the clinical study database. If a subject tests positive to the test they will be excluded from the study.

12.2 Vital Signs

12.2.1 Blood Pressure, Heart Rate and Tympanic Temperature

Blood pressure and heart rate will be measured in supine position after the subject has rested comfortably for at least 5 minutes and in standing position after the subject has stood for 1 minute, using automated Criticon Dynamap® monitors. In Part A at H0 and in Part B at H0 and H8 vital signs will only be assessed in supine position, in order to prevent volunteers from standing up and lying down during infusions. Vital signs (blood pressure and heart rate) will be measured at the time points as detailed in the Study Plan (Table 2 and Table 3). Temperature will be measured using tympanic thermometers.

12.3 Electrocardiographic (ECG) Measurements

12.3.1 Recording of 12-lead ECGs

12-lead ECGs will be recorded at the time-points described in Study Plan (Table 2 and Table 3) using a GE Marquette MAC1200® /MAC1200ST® recorder connected via a fixed network connection to the MUSE® Cardiology Information System (MUSE). ECGs recorded during screening will be stored electronically on the MUSE information system. Only ECG recorded electronically will be valid ECG for any purpose other than safety assessment. ECG printouts may be filed in the subject's CRF for medical safety reviews.

Each ECG recorder will be set up to the required technical specifications and containing the information required to identify the records. Each ECG recording will be clearly identified (Subject ID, visit date, and the actual times of ECG recordings).

12-lead ECG recordings will be made after the subjects have been resting in a supine position for at least 10 minutes. The subjects will avoid postural changes during the ECG recordings and clinical staff will ensure that subjects are awake during the ECG recording.

At each time point, the ECG will be recorded in triplicate, to reduce variance and improve the precision of measurement. The triplicates will be performed at approximately 1-minute intervals. Each ECG recording (trace) will last 10 seconds. Repeat ECG will be performed until at least three 10-second ECG records per scheduled time-point meet the quality criteria set out in the SOM and the applicable SOP so to enable reading and analysing at least 5 complexes per derivation.

All recorded ECG will be reviewed by a Research Physician and the review be documented in the CRF. With regards to the clinical assessment of QTc interval, QTcB will be assessed as this is automatically calculated by the equipment. If there is any indication of potential significant QTcB prolongation, QTcF will also be calculated and assessed by a Research Physician. If a subject shows an abnormal ECG, additional safety recordings (including the use of 5 or 12 lead Holter equipment) may be made and the abnormality be followed to resolution if required. Further details will be included in the SOM.

12.3.2 Real Time Display (ECG Telemetry)

A 12-lead real time ECG will be recorded as described in the Study Plan (Table 2 and Table 3). ECG telemetry will be monitored by the Investigator or qualified member of clinical staff. The system will be managed according to local working practices. The ECG telemetry reports will be archived with study documents.

12.3.3 24-hour Holter ECG

Holter recording will be performed at screening as described in Table 2 and Table 3. If 12-lead holter recording is taken on screening, each electronic Holter ECG file will be downloaded onto the GE Gatemed Holter Analysis system. This will allow the extraction of ten-second 12-lead ECG data files, which can be transferred onto the MUSE. All ECG files so acquired will then be analysed and over-read using the same process as for any other 12-lead ECG.

12.4 Physical Examination, Height and Weight

Physical examinations will be performed as detailed in the Study Plan (Table 2 and Table 3).

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. Measurements should be taken with subjects wearing light clothing and without shoes using calibrated scales for all measurements. BMI will be calculated from the height and weight.

12.5 Pharmacokinetic Assessments

For timing of individual samples refer to the Study Plan (Table 2 and Table 3). The date and time of collection will be recorded on the appropriate CRF.

12.5.1 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 Plan (Table 2 and Table 3). For blood volume see Section 12.7.

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), and the date of transfer or shipment of the samples to the responsible analyst will be documented in detail in the SOM. 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.

12.6 Immunogenicity

The presence of anti-LR12 antibodies will be assessed according to the Study Plan (Table 2 and Table 3). A blood sample will be collected for evaluation of potential immunogenicity evaluation from the appropriate vein for all healthy volunteers at the selected time-points. Sample analysis will be described in the SOM. Further details will be included in the SOM.

12.7 Volume of Blood Sampling

The total volume of blood that will be drawn from each subject in this study will be documented in the SOM and will not exceed 500 mL.

13 ADVERSE EVENTS

Safety will be determined by an evaluation of physical examination, vital signs, ECG parameters, laboratory tests and by the occurrence of 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 rating

The condition of the subjects will be monitored throughout the study. 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 CRF.

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

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

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

The assessment of intensity is outlined in section 8.3.

The causal relationship of an AE to the IMP will be rated as follows:

Unrelated	Clearly and incontrovertibly due only to extraneous causes.
Related	There is a reasonable possibility that the IMP may have caused the AE, i.e. the relationship cannot be ruled out. It may include, for example, a temporal relationship, or a pharmacologically-predicted event. Confounding factors, such as concomitant medications, a concurrent illness or relevant medical history, should also be considered.

The action taken with the IMP for an AE will be rated as: product withdrawn, 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 subject.

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 subject 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.

13.1 Serious Adverse Events (SAE) and Suspected Unexpected Serious Adverse Reaction (SUSAR)

13.1.1 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 subject 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 subject, 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 subject 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.

Pregnancy

Based on the limited reproduction toxicity information, healthy males only will be included.

Suspected Unexpected Serious Adverse Reaction

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

13.1.2 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 subject at each visit/examination must be reported on the respective section of the CRF.

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.

Spontaneously reported SAEs will be collected until 30 days following the final study visit.

SAEs experienced after this 30-day period will only be reported if the investigator suspects a causal relationship with the study drug.

Adverse events (AEs) will be recorded in the CRF throughout the study from day of consent (screening visit) until the last follow up assessment.

Any AEs that are unresolved at the subject'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 subject 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, (tympanic 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 PI.

13.1.3 Reporting of serious adverse events

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

Any SAE/SUSAR will be notified by the Investigator to For Drug Consulting as soon as possible but not later than 24 hours by e-mail or fax to;

E-mail: safety@fordrugconsulting.fr
Phone: +33 (0) 1 46 55 27 11
Fax : +33 (0) 1 47 46 18 48

In addition, the investigator should contact the INOTREM SA Medical Officer.

The initial report will be followed up by a full written report within three working days or five calendar days, whichever comes first unless no further information is available when the follow-up report will be provided as soon as possible when new information becomes available. Further follow-up reports will be provided as and when new information becomes available. 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/SUSAR 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. definitively, 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 SAEs will be included in the INOTREM SA pharmacovigilance database.

SUSARs will be notified to the Competent Authority by For Drug Consulting and to the relevant REC within 7 (for fatal and life-threatening SUSARs) or 15 days (all other SUSARs).

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

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

The detailed procedure of the SAE/SUSAR reporting will be described in a Safety Management Plan that will be finalised before the start of the study to exactly define the different tasks of the Investigator, the Sponsor and RPL (on behalf of the Sponsor)

14 QUALITY ASSURANCE AND QUALITY CONTROL

14.1 Quality Assurance and Quality Control

A regulatory inspection of this study may be carried out by regulatory agencies. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the PI and RPL agree to allow the auditor/inspector direct access to all relevant documents and to allocate their time and the time of their staff to the auditor/inspector to discuss any findings or relevant issues.

Quality Control (QC) procedures at the CPU will be implemented to ensure data recorded into the CRFs are accurate before CRFs are sent for data entry purposes. QC checks will be carried out on critical phases in the execution of the study. These control checks will be carried out according to the relevant SOPs. Records of these procedures will be documented and available for review.

14.2 Monitoring

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.

15 STATISTICAL METHODS PLANNED AND DETERMINATION OF SAMPLE SIZE

15.1 Statistical and Analytical Plans

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

Individual data listings will contain all available results. They will be presented by IMP (LR12 vs Placebo), dose group (Group 1-Group 8), subject number and time point if applicable.

Descriptive statistics will be presented by IMP and time point.

All relevant data will be summarised as follows:

- Quantitative endpoints will be presented in terms of mean, standard deviation, median, Q1, Q3, extreme values, number of subjects and missing data.
- Qualitative endpoints will be presented in terms of number and percentage of each modality and number of subjects and missing data.

For quantitative endpoints, Student test for parametric tests or Wilcoxon test for non-parametric tests will be used.

For qualitative endpoints, Chi-square test for parametric tests or Fisher Exact test for non-parametric tests will be used.

15.1.1 Data Sets Analysed

Randomised set will comprise all randomised subjects.

Safety Set will include all randomised subjects who have taken the IMP, and who have at least one post-baseline assessment of safety, regardless any protocol deviations.

Per Protocol Set will include only the subjects who complete the study according to the protocol.

Subjects' assignment in different sets will be performed during the pre-analysis review meeting.

15.1.2 Demographic and other Baseline Characteristics

Analysis will be performed on the Safety Set.

Baseline characteristics such as demographic characteristics, subject's habits, toxicology, and serology, will be listed and summarised using descriptive statistics already mentioned.

Medical and surgical history, prior therapies will only be listed.

Previous medications will be coded according to the World Health Organization-Drug Reference List (WHO-DRUG dictionary version 2015-3) and will be listed.

Individual safety data (clinical laboratory, vital signs, and ECG) measured before the first drug administration will be checked for validity of entrance criteria, and abnormalities will be documented.

15.1.3 Safety analyses

Adverse events:

Adverse events are coded using the MedDRA dictionary version 18.1 or higher. They are classified by System Organ Class and Preferred Term.

The number and percentage of subjects with at least one adverse event will be provided.

Analysis of treatment-emergent adverse events (TEAE)

Only TEAE will be summarised and described for the following criteria:

- Number and percentages of subjects with at least one TEAE
- Number and percentages of subjects with at least one severe TEAE
- Number and percentages of subjects with at least one study treatment related TEAE
- Number and percentages of subjects with at least one serious TEAE
- Number and percentages of subjects with at least one TEAE leading to treatment withdrawal

The maximum intensity encountered during the evaluation period will be checked.

The number of TEAE of each category will also be provided by system organ class and preferred term.

Analysis of deaths and other serious adverse events

A listing of deaths will be provided.

A summary table of the other serious adverse events should be provided. In case of low incidence of serious adverse events, only a listing will be done.

Vital signs, ECG, physical examination and laboratory data:

Vital signs (SBP, DBP, heart rate, T°), ECG, physical examination and laboratory data will be described at each visit/time. Changes from baseline will be described. Abnormal values will be identified in subject data listings.

Concomitant and other treatments:

Concomitant and other treatments are coded using the WHO-DRUG dictionary version 2014-3. All treatments continued after the inclusion or appeared during the study will be summarised by Anatomical Therapeutic Class (ATC) and substance name.

Anti- LR12 antibodies:

Anti- LR12 antibodies results (positive/negative) will be listed.

15.2 Pharmacokinetics

15.2.1 Evaluation of Pharmacokinetic Parameters

Non-compartmental analysis will be used for estimation of pharmacokinetic parameters using the SAS software. Pharmacokinetic modelling may also be employed to assess potential time-dependent pharmacokinetics.

The following pharmacokinetic parameters will be calculated from measured plasma concentrations of LR12 for each subject and each treatment group:

C_{max} and t_{max}

C_{max} : Maximal plasma concentration

t_{max} : Time at which the maximum plasma concentration occurs

$C_{0.25h}$: Concentration at the end of the loading infusion

C_{8h} : Concentration at the end of the maintenance infusion

$C_{ss\ inf}$: Steady state concentration during the maintenance infusion

Area under the curve (AUC)

$AUC_{(0\text{-}8h)}$ (ng/ml.h) : Area under the plasma concentration-time curve from time 0 to time 8 h

$AUC_{(0\text{-}t)}$ (ng/ml.h) : Area under the plasma concentration curve from administration to last observed concentration at time t measured by trapezoidal rules

$AUC_{(0\text{-}\infty)}$ (ng/ml.h) : Area under the plasma concentration-time curve from time 0 extrapolated to infinite time

[$AUC_{0\text{-}\infty} = AUC_{0\text{-}t} + (C_t/\lambda_z)$, where C_t = the observed concentration of drug for the last sample on the PK profile in which drug was detected, and λ_z as defined below

Plasma concentration half-life

$t_{1/2}$ (h) : Terminal elimination half-life. It will be calculated by application of the equation:

$t_{1/2} = \ln 2/\lambda_z$

λ_z (1/h) : Will be estimated by the linear regression of the logarithm of the terminal concentration as a function of time

CL(L/h/kg) : Apparent systemic clearance

Vd (L/kg) : Apparent volume of distribution (CL/λ_z)

Actual sampling times will be used for all calculations of the PK parameters. If there is any doubt in the actual time a sample was taken, then the scheduled time will be used. Special

consideration will be given to the estimation of λ_z and corresponding $t_{½}$ values. Values of λ_z will be calculated from a minimum of three data points, wherever possible. Any values below the lower limit of quantification (LLOQ) of the assay before the t_{max} will be assumed to be zero. Values below the LLOQ which occur after the t_{max} will be ignored.

15.2.2 Statistical Analysis on PK Parameters

Serum concentrations will be listed and summarised by time point. The PK parameters will be listed for each subject and summarised for each treatment group using descriptive statistics (N - the number of subjects, arithmetic mean, SD - standard deviation, CV - coefficient of variation, geometric mean, median, minimum, maximum).

Analysis of variance models will be applied to the dose normalised and logarithmically transformed pharmacokinetic parameters to investigate possible deviations from dose proportionality.

15.3 Handling of Missing and Incomplete Data

Unrecorded values will be treated as missing. The appropriateness of the method(s) for handling missing data will be reassessed at the data review prior to database lock. Depending on the extent of missing values, further investigation may be carried out into the sensitivity of the analysis results to the method(s) specified.

15.4 Determination of Sample Size

The sample size is based on experience from previous similar Phase I studies. No formal power calculation has been performed and mostly descriptive statistics will be used to summarise safety, pharmacokinetic and pharmacodynamics data.

15.5 Interim Analysis

One interim analysis of safety and PK data is planned, after the treatment phase (Day 2) of cohort 6 is complete. Details will be specified in a separate statistical analysis plan."

16 DATA MANAGEMENT

Data Management will create the database under Oracle (V10.2.04 or higher) and the e-CRF entry screens using Clinsight Ennov Clinical © (V7 or higher) in compliance with the e-CRF design.

The e-CRF 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 e-CRF, and the validation plan.

The investigator, sub-investigators or its designated representative will enter the data for each subject on the Ennov Clinical Online e-CRF application. The data will be extracted from the ORACLE database and formatted as SAS files (V9.4) using Ennov Clinical Export module.

The Data Manager will program the consistency checks defined in the validation plan using Ennov Clinical Test module. These checks will result in the production of Electronic Data Clarification Forms (e-DCFs). The investigator, sub-investigator or its designated representative will directly answer to these e-DCFs on the e-CRF 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.

16.1 Case Report Forms

The e-CRF will be available online, on a secure website (https://ecrf.novasco.fr/CSOnline/). Only the investigators, or the sub-investigators/designee, are authorised to entry data in the e-CRF. 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 e-CRF for each subject having signed the informed consent and randomised. Any additional information on data entry process will be included in the DHP. 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 e-CRF 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 e-CRF, 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 SPONSOR’S AND INVESTIGATOR’S RESPONSIBILITIES

17.1 Sponsor’s Responsibilities

In addition to the responsibilities described in the below sections the Sponsor is responsible to inform the PI of any safety update relating to the IMP.

17.1.1 GCP Compliance

INOTREM SA and any third party to whom aspects of the study management or monitoring have been delegated will undertake their roles for this study in compliance with all applicable regulations and ICH GCP Guidelines.

Visits to the Investigator site will be conducted by representatives of INOTREM SA to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by competent authorities.

17.1.2 Regulatory Approval

INOTREM SA will ensure that Local Competent Authority requirements are met before the start of the study.

17.1.3 Indemnity/Liability and Insurance

INOTREM SA will adhere to the recommendations of the Association of British Pharmaceutical Industry (ABPI) Guidelines. A copy of the Indemnity document will be supplied to the Investigator before study initiation.

INOTREM SA will ensure that suitable insurance cover is in place prior to the start of the study. An insurance certificate and a statement of insurance will be supplied to RPL.

17.1.4 Protocol Management

All protocols and amendments will be prepared by INOTREM SA and/or RPL. If it becomes necessary to issue a protocol amendment during the course of the study, INOTREM SA will notify the Investigator and collect documented Investigator Agreement to the amendment.

17.1.5 End of Trial Notification

INOTREM SA will submit an end of trial notification to the competent authority of the Member State within 90 days of the end of the trial in accordance with EU Directive 2001/20/EC. The PI will be responsible for submitting these to the REC within 90 days of the end of the trial.

For the purposes of this notification, the end of the trial will be defined as the last subject/last visit.

17.1.6 Submission of Summary of Clinical Trial Report to Competent Authorities of Member States Concerned and Regulatory Approval

All the relevant data and information will be reported in a study report prepared by INOTREM and submitted to the investigator for review comments and signature. The final study report will be used for the further development of the IMP and regulatory submissions.

INOTREM SA will provide a summary of the clinical trial report within one year of the end of the complete trial to the competent authority of the Member State concerned as required by

the regulatory requirement and to comply with the Community guideline on Good Clinical Practice.

17.2 Investigator's Responsibilities

17.2.1 GCP Compliance

The Investigator must undertake to perform the study in accordance with ICH GCP Guidelines, EU Directive 2001/20/EC, and the applicable regulatory requirements.

It is the Investigator's responsibility to ensure that adequate time and appropriate resources are available at the study site prior to commitment to participate in this study. The Investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The Investigator will maintain a record of appropriately qualified persons to whom the Investigator has delegated significant trial-related tasks. An up-to-date copy of the *curriculum vitae* for the Investigator, Sub-investigator(s), and essential study staff will be provided to INOTREM SA (or designee) before starting the study.

Agreement with the final Clinical Study Report will be documented by the dated signature of the PI, in compliance with Directive 75/318/EC, Directive 2001/83/EC, and ICH E3.

17.2.2 Protocol Adherence and Investigator Agreement

The PI and delegates must adhere to the CSP as detailed in this document. The PI will be responsible for enrolling only those subjects who have met CSP eligibility criteria. The PI will be required to sign an Investigator Agreement to confirm acceptance and willingness for themselves and delegates to comply with the CSP.

17.2.3 Documentation and Retention of Records

After completion of the study, all documents and data relating to the study will be kept in an orderly manner and securely by the PI in a secure file and/or electronically. The data will be available for inspection by INOTREM SA or their representatives. Essential documents must be retained for 2 years after the final marketing approval in an ICH region or at least 2 years have elapsed since the discontinuation of clinical development of MOTREM. The PI or delegate must contact INOTREM SA before destroying any study-related documentation and it is the responsibility of INOTREM SA to inform the investigative site of when these documents can be destroyed. In addition, all subject records and other source documentation will be kept for a longer period if required by the applicable regulatory requirements.

17.3 Ethical Considerations

This protocol complies with the principles of the World Medical Assembly (Helsinki 1964) and subsequent amendments (10).

17.3.1 Informed Consent

The informed consent is a process by which a subject voluntarily confirms his/her willingness to participate in a clinical study. It is the responsibility of the PI or delegate to obtain written informed consent from subjects. All consent documentation must be in accordance with applicable regulations and GCP. Each subject is requested to sign the Informed Consent Form (ICF) after they have received and read the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject'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 subject or the subject's legally authorised representative. The PI or delegate will provide the Sponsor with a copy of the REC approved consent forms, and a copy of the REC written approval, prior to the start of the study.

17.3.2 Research Ethics Committee (REC) Approval

It is the responsibility of the PI to submit this CSP, the informed consent document (approved by INOTREM SA), relevant supporting information, and all types of subject recruitment information to the REC for review, and all must be approved prior to the start of subject screening. In addition, advertisements must be approved by the REC prior to use at the site. Prior to implementing changes in the study, INOTREM SA and the REC must also approve any substantial amendments to the CSP and corresponding updates to informed consent documents. For non-substantial protocol amendments (that do not require REC approval) and subsequent updates of the ICF all changes will be done in agreement with INOTREM SA and RPL.

17.4 Confidentiality

Data collected during this study may be used to support the development, registration, or marketing of medicinal product. INOTREM SA will control all data collected during the study, and will abide by the EU Directive on Data Privacy concerning the processing and use of subjects' personal data. For the purpose of data privacy legislation, INOTREM SA will be the data controller.

After subjects have consented to take part in the study, their medical records and the data collected during the study will be reviewed by INOTREM SA and/or its representatives. These records and data may, in addition, be reviewed by the following: independent auditors who validate the data on behalf of INOTREM SA; national or local regulatory authorities, and the REC which gave its approval for this study to proceed.

Although subjects will be known by a unique number, their initials and date of birth will also be collected and used to assist INOTREM SA to verify the accuracy of the data, for example, that the results of study assessments are assigned to the correct subject. The results of this study containing the unique number, initials, date of birth, 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 INOTREM SA in such countries.

17.5 Publication Policy

If the investigator wishes to publish or present the results of this study, the sponsor must be informed to in due time before the submission of any confidential information to an editorial board or scientific review committee. This will enable the sponsor to protect its proprietary information from disclosure to the public, and to provide comments based on information which may not yet be available to the investigator.

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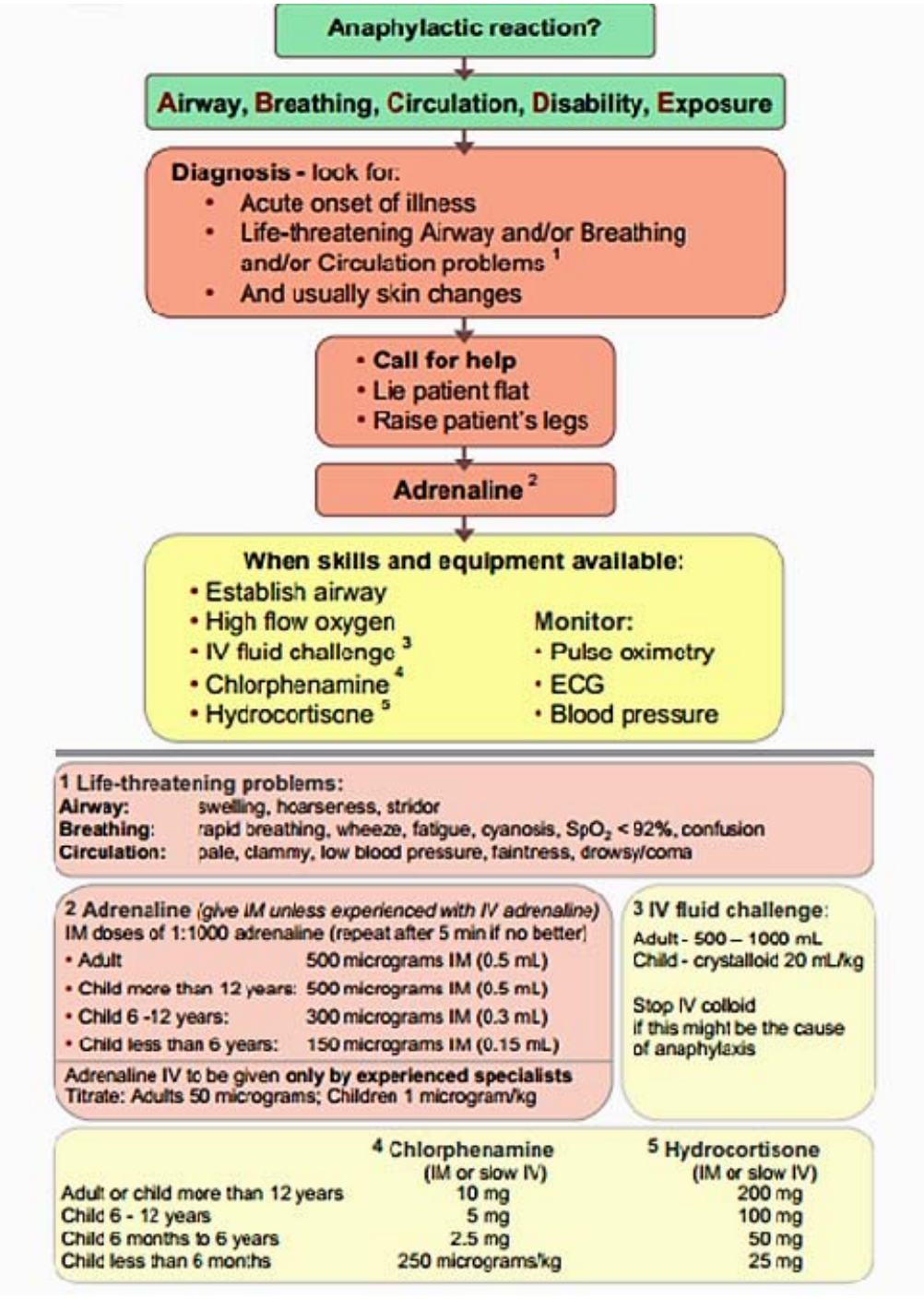
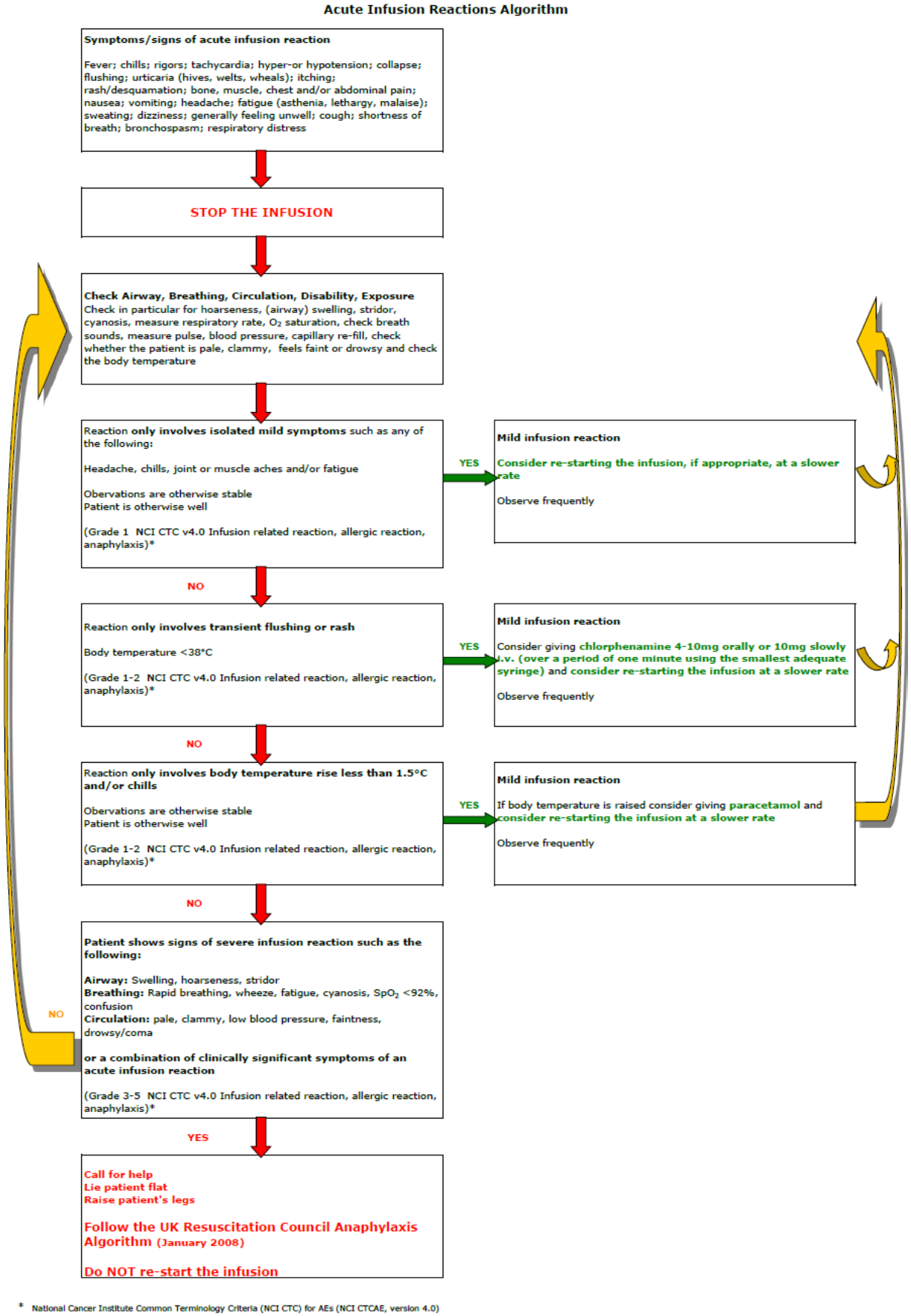
19 APPENDICES

19.1 UK Treatment Guideline for Anaphylaxis



Source: Emergency treatment of anaphylactic reactions - Guidelines for healthcare providers. Annotated with links to NICE guidance July 2012 (11)

19.2 Acute Infusion Reactions Algorithm



* National Cancer Institute Common Terminology Criteria (NCI CTC) for AEs (NCI CTCAE, version 4.0)

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STUDY PROTOCOL

Non-Substantial Amendment 2

A Phase I, randomised, placebo controlled study to assess the safety, tolerability and pharmacokinetic profiles of ascending, single, intravenous doses of MOTREM (LR12) in healthy male subjects

Investigational medicinal product: MOTREM (LR12)
Development phase: Ia

Version: 1.0 Final
Date: 03 May 2016

Sponsor Study Code:	MOT-C-104
CRO Study Code	C15030
EudraCT Number	2015-005654-35
Sponsor	INOTREM SA 114 Rue La Boétie 75008 Paris, France
Sponsor's Officer	Jean-Jacques GARAUD, MD Chief Executive Officer 114 Rue La Boétie 75008 Paris, France
Principal Investigator	Dr Ulrike Lorch, MD FRCA FFPM Richmond Pharmacology Ltd. St George's University of London Cranmer Terrace, Tooting London SW17 0RE, UK
Study Site	Richmond Pharmacology Ltd. Croydon University Hospital, Thornton Wing, 530 London Road, Croydon, CR7 7YE, UK

Amendment [Non-Substantial] 2 Signature Page

Protocol No: MOT-C-104:

A Phase I, randomised, placebo controlled study to assess the safety, tolerability and pharmacokinetic profiles of ascending, single, intravenous doses of MOTREM (LR12) in healthy male subjects

This protocol amendment has been subjected to an internal Inotrem SA peer review.

I agree to the terms of this protocol amendment (non-substantial).

Sponsor's Signatories:

Jean-Jacques GARAUD, MD, INOTREM
Sponsor's Officer

Signature: _____ **Date:** 4 May, 2016

Valérie CUVIER, INOTREM
Project Manager

Signature: _____ **Date:** 4 May, 2016

Principal Investigator Signature:

I agree to the terms of this protocol amendment dated 03 May 2016. I will conduct the trial according to the procedures specified herein, and according to the principles of Good Clinical Practice and local regulations.

Principal Investigator:
Dr Ulrike Lorch, MD FRCA FFPM

Signature: U. Lorch **Date:** 04 MAY 2016

Reason for Amendment:

1. The purpose of this amendment is to gather additional pharmacokinetic information. The amendment describes a 100% extension of Group 2 (Part A) in line with the Adaptive feature no 8, Limit I-III. Subject 202 will participate in Part A, group 2 and will be administered an intravenous MOTREM (LR12) dose of 10 mg over 15 min for further evaluation of the pharmacokinetic profile at the selected dose regimen. Three additional pre-dose blood samples will be obtained and processed in accordance with the Adaptive feature no 13 Limit I & II from the volunteer. These changes will not affect the volunteers' safety.

Inotrem SA considers this amendment to be non-substantial.

Persons who initiated the Amendment

Inotrem SA and Richmond Pharmacology Ltd

Sponsor:

INOTREM SA, 114 Rue La Boétie, 75008 Paris, France

Centres affected by the Amendment:

Richmond Pharmacology Ltd, UK

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STUDY PROTOCOL

Non-Substantial Amendment 3

A Phase I, randomised, placebo controlled study to assess the safety, tolerability and pharmacokinetic profiles of ascending, single, intravenous doses of MOTREM (LR12) in healthy male subjects

Investigational medicinal product: MOTREM (LR12)
Development phase: Ia

Version: 1.0
Date: 12 May 2016

Sponsor Study Code:	MOT-C-104
CRO Study Code	C15030
EudraCT Number	2015-005654-35
Sponsor	INOTREM SA 114 Rue La Boétie 75008 Paris, France
Sponsor's Officer	Jean-Jacques GARAUD, MD Chief Executive Officer 114 Rue La Boétie 75008 Paris, France
Principal Investigator	Dr Ulrike Lorch, MD FRCA FFPM Richmond Pharmacology Ltd. St George's University of London Cranmer Terrace, Tooting London SW17 0RE, UK
Study Site	Richmond Pharmacology Ltd. Croydon University Hospital, Thornton Wing, 530 London Road, Croydon, CR7 7YE, UK

Amendment [Non-Substantial] 3 Signature Page

Protocol No: MOT-C-104:

A Phase I, randomised, placebo controlled study to assess the safety, tolerability and pharmacokinetic profiles of ascending, single, intravenous doses of MOTREM (LR12) in healthy male subjects

This Clinical Trial protocol and amendment have been subjected to an internal Inotrem SA peer review.

I agree to the terms of this protocol amendment (non-substantial).

Sponsor's Signatories:

Jean-Jacques GARAUD, MD, INOTREM
Sponsor's Officer

Signature: _____ **Date:** May 12 201

Valérie CUVIER, INOTREM
Project Manager

Signature: _____ **Date:** May 12, 2016

Principal Investigator Signature:

I agree to the terms of this protocol and the amendment dated 12 May 2016. I will conduct the trial according to the procedures specified herein, and according to the principles of Good Clinical Practice and local regulations.

Principal Investigator:
Dr Ulrike Lorch, MD FRCA FFPM

Signature: U. Lorch **Date:** 13 MAY 2016

Reason for Amendment:

1. The purpose of this amendment is to reduce the number of PK samples in line with the Adaptive feature no 13 Limit I & II. The change in PK sampling does not affect other assessments which can be performed at the same time as per the previous protocol.

The following changes to the protocol version 2.0 dated 22 February 2016 were implemented:

Previous text

Table 3

Pharmacokinetics on Day 1 H0: T5', ~~T10',~~ T15', T18', ~~T21', T25',~~ T30', T45'

Revised text

Table 3

Pharmacokinetics on Day 1 H0: T5', T15', T18', T30', T45'

Previous text

Table 3

Pharmacokinetics on Day 1 H8: ~~T-5~~, T2, T4', T7', ~~T11'~~, T15', ~~T20'~~

Revised text (inserted text in bold)

Table 3

Pharmacokinetics on Day 1 H8: **T-15'**, T2, T4', T7', T15', **T30'**

Inotrem SA considers this amendment to be non-substantial.

Persons who initiated the Amendment

Inotrem SA and Richmond Pharmacology Ltd

Sponsor:

INOTREM SA, 114 Rue La Boétie, 75008 Paris, France

Centres affected by the Amendment:

Richmond Pharmacology Ltd, UK

STUDY PROTOCOL

Non-Substantial Amendment 4

A Phase I, randomised, placebo controlled study to assess the safety, tolerability and pharmacokinetic profiles of ascending, single, intravenous doses of MOTREM (LR12) in healthy male subjects

Investigational medicinal product: MOTREM (LR12)
Development phase: Ia

Version: 1.0
Date: 22 July 2016

Sponsor Study Code:	MOT-C-104
CRO Study Code	C15030
EudraCT Number	2015-005654-35
Sponsor	INOTREM SA 114 Rue La Boétie 75008 Paris, France
Sponsor's Officer	Jean-Jacques GARAUD, MD Chief Executive Officer 114 Rue La Boétie 75008 Paris, France
Principal Investigator	Dr Ulrike Lorch, MD FRCA FFPM Richmond Pharmacology Ltd. St George's University of London Cranmer Terrace, Tooting London SW17 0RE, UK
Study Site	Richmond Pharmacology Ltd. Croydon University Hospital, Thornton Wing, 530 London Road, Croydon, CR7 7YE, UK

Amendment [Non-Substantial] 4 Signature Page

Protocol No: MOT-C-104:

A Phase I, randomised, placebo controlled study to assess the safety, tolerability and pharmacokinetic profiles of ascending, single, intravenous doses of MOTREM (LR12) in healthy male subjects

This protocol amendment has been subjected to an internal Inotrem SA peer review.

I agree to the terms of this protocol amendment (non-substantial).

Sponsor's Signatories:

Jean-Jacques GARAUD, MD, INOTREM
Sponsor's Officer p.o. MARGARITA SALCEDO, CDO

Signature: _____ **Date:** 25-07-2016

Valérie CUVIER, INOTREM
Project Manager

Signature: _____ **Date:** 25.07.2016

Principal Investigator Signature:

I agree to the terms of this protocol amendment dated 22 July 2016. I will conduct the trial according to the procedures specified herein, and according to the principles of Good Clinical Practice and local regulations.

Principal Investigator:
Dr Ulrike Lorch, MD FRCA FFPM

Signature: U. Lorch **Date:** 25 JUL 2016

Reason for Amendment:

1. The purpose of this amendment is to adjust the maintenance dose increment between cohort 7 and cohort 8 to a factor of 2. The amendment describes the administration of a 6 mg/kg/h maintenance dose to cohort 8 in line with Adaptive Feature number 1, limit VII, Adaptive Features 2 and 3 Limits I and III.

   The current approved protocol for the study MOT-C-104 (version 3.0 dated 13 May 2016) foresees an increment of 3 for the maintenance dose in all cohorts of Part B and progression to the maintenance dose of 9 mg/kg/h (over 7 hours and 45 minutes) in cohort 8.

   Since the dose of 9 mg/kg/h is not planned for therapeutic use and was only foreseen to document the safety of the product, a reduced maintenance dose of 6 mg/kg/h is considered sufficient for documenting the safety of the product in healthy volunteers considering the currently available data. The Safety Review Committee agreed to escalate to the cohort 8 with an increment of 2 rather than 3 and thus give 6 mg/kg/h for 7 hours 45 minutes.

   These changes will not affect the volunteers' safety.

Sections of the protocol affected:

1. **Section 5 Study Synopsis**

Old text

Part B:

Group 3: 0.5 mg/kg i.v. loading dose and 0.03 mg/kg/h maintenance dose i.v. over 7 hours and 45 min;

Group 4: 1 mg/kg i.v. loading dose and 0.1 mg/kg/h maintenance dose i.v. over 7 hours and 45 min;

Group 5: 2 mg/kg i.v. loading dose and 0.3 mg/kg/h maintenance dose i.v. over 7 hours and 45 min;

Group 6: 5 mg/kg i.v. loading dose and 1 mg/kg/h maintenance dose i.v. over 7 hours and 45 min;

Group 7: 5 mg/kg i.v. loading dose and 3 mg/kg/h maintenance dose i.v. over 7 hours and 45 min;

Group 8: 5 mg/kg i.v. loading dose and 9 mg/kg/h maintenance dose i.v. over 7 hours and 45 min.

Please refer to Table 1.

Revised text (deleted text is shown as a strikethrough and inserted text is in bold and underlined)

Part B:

Group 3: 0.5 mg/kg i.v. loading dose and 0.03 mg/kg/h maintenance dose i.v. over 7 hours and 45 min;

Group 4: 1 mg/kg i.v. loading dose and 0.1 mg/kg/h maintenance dose i.v. over 7 hours and 45 min;

Group 5: 2 mg/kg i.v. loading dose and 0.3 mg/kg/h maintenance dose i.v. over 7 hours and 45 min;

Group 6: 5 mg/kg i.v. loading dose and 1 mg/kg/h maintenance dose i.v. over 7 hours and 45 min;

Group 7: 5 mg/kg i.v. loading dose and 3 mg/kg/h maintenance dose i.v. over 7 hours and 45 min;

Group 8: 5 mg/kg i.v. loading dose and ~~9~~ **6** mg/kg/h maintenance dose i.v. over 7 hours and 45 min.

Please refer to Table 1.

2. **Section 10.1.1 Doses and Treatment Regimen**

Old text

Single doses of MOTREM (LR12) or matching placebo are planned to be administered i.v. as detailed in Table 11.

Table 11. Daily dose of IMP (MOTREM or matching placebo) for each dose group.

Dose group	i.v. loading dose T = 15'	Maintenance i.v. dose (mg/kg/h) T = 7h45'	Number of subjects
Group 1	1 mg	-	N = 1
		-	
Group 2	10 mg	-	N = 1
		-	
Group 3	0.5 mg/kg	0.03 mg/kg/h	N = 3
	Placebo	Placebo	N = 1
Group 4	1 mg/kg	0.1 mg/kg/h	N = 3
	Placebo	Placebo	N = 1
Group 5	2 mg/kg	0.3 mg/kg/h	N = 3
	Placebo	Placebo	N = 1
Group 6	5 mg/kg	1 mg/kg/h	N = 3
	Placebo	Placebo	N = 1
Group 7	5 mg/kg	3 mg/kg/h	N = 3
	Placebo	Placebo	N = 1
Group 8	5 mg/kg	9 mg/kg/h	N = 3
	Placebo	Placebo	N = 1

Revised text (deleted text is shown as a strikethrough and inserted text is in bold and underlined)

Single doses of MOTREM (LR12) or matching placebo are planned to be administered i.v. as detailed in Table 11.

Table 11. Daily dose of IMP (MOTREM or matching placebo) for each dose group.

Dose group	i.v. loading dose T = 15'	Maintenance i.v. dose (mg/kg/h) T = 7h45'	Number of subjects
Group 1	1 mg	-	N = 1
		-	
Group 2	10 mg	-	N = 1
		-	
Group 3	0.5 mg/kg	0.03 mg/kg/h	N = 3
	Placebo	Placebo	N = 1
Group 4	1 mg/kg	0.1 mg/kg/h	N = 3
	Placebo	Placebo	N = 1
Group 5	2 mg/kg	0.3 mg/kg/h	N = 3
	Placebo	Placebo	N = 1
Group 6	5 mg/kg	1 mg/kg/h	N = 3
	Placebo	Placebo	N = 1
Group 7	5 mg/kg	3 mg/kg/h	N = 3
	Placebo	Placebo	N = 1
Group 8	5 mg/kg	**6** ~~9~~ mg/kg/h	N = 3
	Placebo	Placebo	N = 1

Inotrem SA considers this amendment to be non-substantial as it applies the protocol approved adaptive features and their limits.

Persons who initiated the Amendment

Inotrem SA and Richmond Pharmacology Ltd

Sponsor:

INOTREM SA, 114 Rue La Boétie, 75008 Paris, France

Centres affected by the Amendment:

Richmond Pharmacology Ltd, UK