A Phase II Double-blind, Randomised, Parallel Group 2:1 Comparison of the Efficacy and Safety of FP-1201-lyo (Recombinant Human Interferon beta-1a) and Placebo in the Prevention of Multi-Organ Failure on Patients Surviving Open Surgery for a Ruptured Abdominal Aortic Aneurysm

NCT03119701

Protocol Version: 05

Protocol Date: 16 Apr 2019

FARON
Pharmaceuticals

TITLE: A Phase II Double-blind, Randomised, Parallel Group 2:1 Comparison of the Efficacy and Safety of FP-1201-lyo (Recombinant Human Interferon beta-1a) and Placebo in the Prevention of Multi-Organ Failure on Patients Surviving Open Surgery for a Ruptured Abdominal Aortic Aneurysm

INFORAAA study

Sponsor:	Faron Pharmaceuticals Ltd Joukahaisenkatu 6 FIN-20520 Turku Finland
Co-ordinating Investigators	[redacted]
Sponsor Protocol No.:	FP1CLI006
EudraCT No.:	2014-000899-25
Study Drug Name:	FP-1201-lyo
Development Phase:	II
Date of Protocol:	16 Apr 2019, Version 05

NCT03119701

The study will be conducted according to the protocol and in compliance with Good Clinical Practice, with the Declaration of Helsinki and with other applicable regulatory requirements.

SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title: A Phase II Double-blind, Randomised, Parallel Group 2:1 Comparison of the Efficacy and Safety of FP-1201-lyo (Recombinant Human Interferon beta-1a) and Placebo in the Prevention of Multi-Organ Failure on Patients Surviving Open Surgery for a Ruptured Abdominal Aortic Aneurysm

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, as amended in 2013, and the ICH guidelines on Good Clinical Practice.

[redacted]

[redacted]

Date

[redacted]

Faron Pharmaceuticals Ltd

Declaration of the Co-ordinating Investigators

Title: A Phase II Double-blind, Randomised, Parallel Group 2:1 Comparison of the Efficacy and Safety of FP-1201-lyo (Recombinant Human Interferon beta-1a) and Placebo in the Prevention of Multi-Organ Failure on Patients Surviving Open Surgery for a Ruptured Abdominal Aortic Aneurysm

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, as amended in 2013, and the ICH guidelines on Good Clinical Practice.

Co-ordinating Investigators

[redacted]

[redacted]

Date

[redacted]

Date

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Co-ordinating Investigators

[redacted] Date

[redacted] Date

Declaration of the National Co-ordinating Investigator

Title: A Phase II Double-blind, Randomised, Parallel Group 2:1 Comparison of the Efficacy and Safety of FP-1201-lyo (Recombinant Human Interferon beta-1a) and Placebo in the Prevention of Multi-Organ Failure on Patients Surviving Open Surgery for a Ruptured Abdominal Aortic Aneurysm

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National Co-ordinating Investigator

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number

Declaration of the Investigator

Title: **A Phase II Double-blind, Randomised, Parallel Group 2:1 Comparison of the Efficacy and Safety of FP-1201-lyo (Recombinant Human Interferon beta-1a) and Placebo in the Prevention of Multi-Organ Failure on Patients Surviving Open Surgery for a Ruptured Abdominal Aortic Aneurysm**

All documentation for this study that is supplied to me, and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, electronic Case Report Form, and other scientific data.

The study will not commence without a prior written approval of a properly constituted Independent Ethics Committee (IEC). No substantial changes will be made to the study protocol without a prior written approval of the Sponsor and the IEC, except where necessary to eliminate an immediate hazard to the patients.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Investigator of the local study centre

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number

PROTOCOL SYNOPSIS

Title	A Phase II Double-blind, Randomised, Parallel Group 2:1 Comparison of the Efficacy and Safety of FP-1201-lyo (Recombinant Human Interferon beta-1a) and Placebo in the Prevention of Multi-Organ Failure on Patients Surviving Open Surgery for a Ruptured Abdominal Aortic Aneurysm
Sponsor Study No.	FP1CLI006
Phase	II
Sponsor	Faron Pharmaceuticals Ltd
Co-ordinating Investigators	[redacted]
Study Centre(s)	Approximately 10-18 investigational sites located in Finland, UK, Lithuania and Estonia and possibly in other EEA countries and in USA will participate in the study.
Objectives	
Primary Objective	To evaluate the efficacy and safety of FP-1201-lyo over placebo on all-cause mortality at study day 30; D30 (30 days from the first dose of the study medication).
Secondary Objectives	**1.** To evaluate the efficacy of FP-1201-lyo treatment by assessing short term outcomes (D30) and mid-term outcomes (D90 [3 months]) **2.** To evaluate the safety and tolerability of FP-1201-lyo treatment **3.** To evaluate the pharmacodynamics (PD) of FP-1201-lyo **4.** To evaluate the Tentative Disease Specific Marker CD73 and Potential Inflammatory Markers (PIM) **5.** To evaluate neutralizing antibodies against IFN beta-1a (NAbs)
Efficacy	**Primary Efficacy Endpoint:** • All-cause mortality at D30 **Secondary Efficacy Endpoints:** • All-cause mortality at D90 (3 months) • Number of ventilator free days (VFDs) at D30 • Number of days receiving haemodialysis at D30 and D90 • Number of organ failure free days up to D30 by

	means of the SOFA score • Prevalence of abdominal compartment syndrome, i.e. intra-abdominal pressure (IAP) between study groups • Neutralizing antibodies against IFN beta-1a (NAbs) in whole blood samples up to D30 • Disability on D90 measured by modified ranking scale (mRS)
Safety	• Clinically significant treatment emergent adverse events (TEAEs) up to D30 from vital signs data, laboratory data, physical examinations and spontaneous reporting when conscious
Pharmacoeconomics	• Length of ICU stay, in terms of ICU free days at D30 • Length of hospital stay, in terms of hospital free days at D90 • Length of stay at another health care facility at D90 • Length of haemodialysis needed • Ventilation free days at D30
Pharmacodynamics (PD)	• MxA (protein) concentration in whole blood samples from baseline up to D13
Tentative Disease Specific Marker	• CD73 concentration/activity in serum samples from baseline up to D13 • Potential Inflammatory Markers (IL-6 and HGF) in serum samples from baseline up to D13
Design	Multicentre, randomised, double-blinded, Phase II, parallel group comparison study of the efficacy and safety of FP-1201-lyo compared to placebo in patients surviving emergency open surgery for an infra-renal ruptured abdominal aortic aneurysm. Receiving as post-surgical preventive treatment either FP-1201-lyo or placebo. Both treatment groups will receive standard supportive care.

Treatment	10µg FP-1201-lyo or placebo will be administered daily every 24 hrs for 6 days (D0 D5). The first dose will be given after successful surgery at the point when the patient arrives to the ICU. No dose modifications or short interruptions of study treatment are allowed. Retreatment with a second course of study medication is not permitted.
Number of patients	With an estimated screening failure rate of approximately 15%, 180 patients diagnosed with a ruptured abdominal aortic aneurysm requiring and eligible for immediate open aortic repair will be consented and entered into the study in order to randomise and initiate treatment of 152 patients. For the final analysis, a minimum of 129 evaluable patients will be required (excluding early deaths). There is a possibility of early stopping for efficacy or futility after at least 31 and 84 evaluable patients based on interim analysis. The sample size calculations will be re-evaluated after the first interim analysis has been performed.
Inclusion Criteria:	To be eligible for inclusion into this study, each patient must fulfil the following inclusion criteria **during screening <u>and</u> prior to the first dose of the study medication being administered on D0 (criteria 1 or 2 and all 3, 4 and 5)**: **1.** Patients (male or female) presenting with a ruptured abdominal aortic aneurysm (RAAA) diagnosed by ultrasound or CT-scan in the emergency room • all forms of infrarenal RAAAs with or without coexisting iliac aneurysms are included or **2.** Patients (male or female) presenting with symptoms of RAAA known to have an infrarenal AAA and proceeding straight to open repair without radiological assessment and confirmed rupture (retroperitoneal haematoma) in operation and **3.** Aneurysma repair must be infra-renal, i.e. the proximal anastomosis must be below the renal arteries and the renal arteries must stay intact. Temporary above the renal clamping can be used for a maximum of 30 minutes (total clamping time)

and

4. Patients or their next of kin providing informed consent (written signed or witnessed)

and

5. Age of 18 years or higher

Exclusion Criteria:

To be eligible for inclusion into this study, each patient must not meet any of the following exclusion criteria during screening or prior to the first dose of the study medication being administered:

1. Moribund patient not eligible for treatment in ICU or expected to survive surgery
2. Markedly short life expectancy, e.g. advanced malignant disease
3. Current participation in another experimental treatment protocol
4. Significant congestive heart failure, defined as New York Heart Association (NYHA) class IV
5. Current treatment with IFN alpha or IFN beta
6. Dialysis therapy for chronic renal failure
7. Irreversible shock from haemorrhage
8. Unconsciousness when arriving to the hospital and during screening
9. rEVAR first (prior attempt for endovascular aortic repair for the current rupture)
10. Diagnosed cirrhosis
11. Pregnancy and women with child bearing potential without a negative pregnancy test
12. Rupture not confirmed by CT or intra-operatively (impending ruptures are excluded)
13. RAAA requiring repair of the renal arteries or proximal aorta
    - thoracoabdominal aneurysms requiring immediate repair
    - damaged renal arteries during emergency clamping requiring repair

    NOTE:

    - temporary clamping above the renal arteries (max 30 min total clamping time above the renal arteries) **does not** lead to exclusion

- ligation of the left renal vein **does not** lead to exclusion

Statistical Method:

152 randomised and treated patients are needed to achieve the sample size of 129 evaluable patients for the primary efficacy endpoint. The sample size calculations will be re-evaluated after the first interim analyses.

Standard statistical methods will be used in the primary efficacy outcome analyses. Logistic regression model will be used for the analyses of observed mortality rates in the two treatment groups. Stratification factors used in the randomisation will be included in the model.

Data for the primary efficacy endpoint will also be presented for key, pre-defined subgroups of patients. Mortality at D30 will be illustrated also using survival function and Kaplan-Meier curves including log-rank test as an exploratory analysis.

Analysis Sets:

The Full Analysis Set for efficacy (FAS-E) will consist of all randomised patients excluding early deaths (within 36 hours from treatment initiation) and will be the analysis set on which the primary efficacy analysis will be based.

The Per Protocol Set (PPS) will consist of those patients in the FAS-E excluding patients with major protocol violations. A relevant list of major protocol violations will be detailed in the SAP. The precise definition of the PPS at patient level will be identified at the blind review.

Statistical analyses for the primary and secondary endpoints will be performed on both the FAS-E and PPS.

The Full Analysis Set for safety (FAS-S) will consist of all patients who receive at least one dose of study medication and will be the analysis set on which all safety and tolerability analyses will be based. A patient receiving the wrong treatment according to the randomisation will be analysed for safety and tolerability in the treatment group corresponding to the treatment received.

Interim Analyses:

Interim analysis will be performed after there are at least 31 and 84 evaluable patients for the primary efficacy endpoint analysis. At this point the study can be stopped for efficacy or futility depending on the interim analysis results. The first interim is brought further up as the recruitment rate has markedly stagnated, mainly due to changes in treatment practices of RAAA. The sample size calculations will be re-evaluated after the first interim analysis.

Independent data monitoring committee (IDMC)	IDMC consist of key opinion leaders in scientific field and is responsible for overlooking the overall safety of the study. IDMC is obliged to discontinue the study, if the benefit risk balance is negative.

LIST OF STUDY PERSONNEL

Sponsor

[redacted]

Faron Pharmaceuticals Ltd
Joukahaisenkatu 6
FIN-20520 Turku, Finland

[redacted]

Co-ordinating Investigators

[redacted]

Contract Research Organisation

[redacted]

Safety Reporting

[redacted]

Central Laboratory for Analysis of Neutralising Antibodies to IFN beta-1a, MxA and CD73

[redacted]

Central Laboratory for Analysis of HGF and IL-6

[redacted]

Drug Supply

Data Management and Statistical Analyses

TABLE OF CONTENTS

Tables

Figures

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
ALAT	Alanine Transaminase (SGPT)
ALI	Acute Lung Injury
ARDS	Acute Respiratory Distress Syndrome
ASAT	Aspartate Transaminase (SGOT)
BIPAP	Bilevel Positive Airway Pressure
BP	Blood Pressure
CI	Confidence Interval
CPAP	Continuous Positive Airway Pressure
CRA	Clinical Research Associate
eCRF	Electronic Case Report Form
CRO	Contract Research Organisation
CT	Computerised Tomography
D	Day (as in treatment day/postoperative day)
dl	Decilitre
ER	Emergency room
FAS	Full Analysis Set
FiO2	Fraction of Inspired Oxygen
GCS	Glasgow Coma Scale
HR	Heart Rate
hr	Hour
IAP	Intra-abdominal pressure
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	Interferon
IWRS	Interactive Web Response System
kg	Kilogram
l	Litre
MAP	Mean Airway Pressure
MedDRA	Medical Dictionary for Regulatory Activities
min	Minutes
ml	Millilitre
mm	Millimetre
mmHg	Millimetres of mercury
mol	Mole
MxA	Myxovirus Resistant Protein A
NAbs	Neutralizing antibodies
NYHA	New York Heart Association
OR	Operation Room
P	Pulse
PaO_2	Partial Pressure of Oxygen
PD	Pharmacodynamic
PICD	Patient Informed Consent Document

PPS	Per Protocol Set
PS	Pressure Support
RAAA	Ruptured abdominal aortic aneurysm
rEVAR	Ruptured Endovascular Aortic Repair
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
UAB	Unassisted Breathing
VFD	Ventilator Free Days
WFI	Water for Injection

1 INTRODUCTION

This is a Phase II clinical study to investigate the efficacy and safety of FP-1201-lyo (Recombinant Human Interferon [IFN] beta-1a) in patients surviving emergency open surgery for an infrarenal ruptured abdominal aortic aneurysm. FP-1201-lyo is a lyophilised powder form of Recombinant Human IFN beta-1a reconstituted in water for injection and is administered intravenously as a bolus injection for 6 consecutive days.

1.1 Disease review and rationale for the study

Ruptured abdominal aortic aneurysm (RAAA) is a surgical emergency with an overall mortality of 70 80 % (Bown et al. 2002). It requires immediate surgery and aortic repair. Approximately half of RAAA patients do not reach the hospital and despite immediate surgery and intensive care treatment another half of the patients die in hospital within 30 days post-operatively mostly due to multi-organ failure. Surviving RAAA patients have a long-life expectancy comparable to that of their age group (Alric et al. 2003, Korhonen et al. 2003 and Biancari et al. 2011). The cause of high post-operative mortality is in part due to prolonged hypotension from the ruptured aorta and the aftermath of restoring blood flow; reperfusion, vascular leakage and failure of vital organs. Diagnosed primary causes of post-operative mortality are acute renal failure, intestinal infarction, myocardial infarction, respiratory insufficiency and multi-organ failure (Bown et al. 2004).

Despite several decades of RAAA surgery and advancements in modern medicine surprisingly little has been achieved in reducing post-operative mortality (Bown et al. 2001 and Vänni et al. 2016). A major advancement benefiting the patients has been the minimisation of the time of hypotension, i.e. the time from rupture to clamping of the aorta. For several decades intra-operative mortality has remained rather small and constant, at around 3,5 %. Post-operative mortality has shown a slight decline over the decades but still remains high at around 25 50 % depending on patient cohorts. Recently very significant publications have been made on the mortality of RAAA, because endovascular aortic repair (EVAR) has been suggested a promising treatment without major surgical trauma and lower mortality. Open and endovascular aortic repair for a rupture (rEVAR) have been studied against each other in both prospective randomized settings and registry based studies, but no clear significant difference has been seen in mortality rates (IMPROVE trialists 2014 and Karthikesalingam et al. 2014). Thus, we can now state that due to the overall haemorrhagic shock and ischemia-reperfusion injury leading to a systemic inflammatory response syndrome (SIRS) and multi-organ failure (MOF) the mortality of RAAA is very precisely around 30-35%, which also applies to Finland (Kantonen et al. 1999, Biancari et al. 2011 and Vänni et al. 2016).

Even in elective non-emergency AAA repair, patients experience a SIRS due to clamping and unclamping of the aorta (Bown et al. 2001). Compared to patients undergoing endovascular repair for a ruptured aneurysm patients undergoing open repair are considered to suffer from a two-fold SIRS strain due to the initial rupture and then the open surgery involving clamping and un-clamping of the aorta (Makar et al. 2013). In addition, preliminary human data has shown that cross-clamping the infra-renal aorta is associated with decreased CD73 activity in post-operative serum samples, which implies that hypoxia and CD73 mediated compensatory mechanisms are impaired or adapt too slowly to the ischemic insult (Jalkanen et al. 2016). This

implies that any drug substance that could enhance the natural response to hypoxia by increasing CD73 activity mediated adenosine production, could be beneficial against hypoxia-induced inflammation and increased capillary leakage (Eltzschig et al. 2012).

It has been well established that CD73 expression and it's ecto-5'-nucleotidase activity can be induced by IFN beta in cultured endothelial cells with a consequent decrease in vascular permeability (Niemelä et al. 2004). IFN beta-1a has already been demonstrated as safe and effective in the treatment of ARDS patients in the FPCLI001 study, with a similar underlying pathological molecular mechanism (Bellingan et al. 2014). Thus, FP-1201-lyo offers a promising treatment for CD73 and adenosine regulated post-ischemic injury not in one but several organs under risk during operative treatment of RAAA.

1.2 Investigational medicinal product

Recombinant Human IFN beta-1a is an approved treatment for patients with relapsing remitting multiple sclerosis and the safety profile in such patients is well characterised. More recently Recombinant Human IFN beta-1a was assessed for the treatment of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) in a phase I/II study (FPCLI001). According to the FPCLI001 study ARDS patients receiving IFN beta-1a benefited substantially (Bellingan et al. 2014). Based on dose findings, 10 µg i.v. daily dose of IFN beta-1a for 6 consecutive days was found to be the optimal tolerated dose with a good safety profile in this severely ill patient population of ALI/ARDS.

FP-1201-lyo is a lyophilised powder form of Recombinant Human IFN beta-1a reconstituted in water. Additionally, FP-1201-lyo has been investigated in Japanese moderate/severe ARDS patients with comparable results to FPCLI001 study (final study report pending).

Based on the phase I/II study (FPCLI001) dose finding, it is expected that the 10 µg i.v. daily dose of FP-1201-lyo for 6 consecutive days would be optimal also in RAAA patients, the same dose as in undergoing phase III trial in moderate/severe ARDS (INTEREST trial).

1.3 Mechanism of Action

CD73 is an ecto-5'-nucleotidase enzyme expressed on vascular endothelium, epithelial cells and on a subset of leukocytes (Zimmermann et al. 1992). Through dephosphorylation of adenosine monophosphate (AMP), it yields adenosine, a potent anti-inflammatory molecule, which prevents vascular leakage and inhibits leukocyte recruitment into sites of inflammation (Colgan et al. 2006). Such endogenous protective mechanisms are enhanced in the presence of hypoxia (Thompson et al. 2004). CD73 expression on immune and vascular cells and extracellular adenosine production have been linked to the alleviation of ischemia-reperfusion injury of the myocardium, intestine and kidneys in preclinical settings.

Preclinical studies have shown that CD73 expression is up-regulated in the endothelium by IFN beta-1a treatment in a time and dose dependent fashion (Niemelä et al. 2004). Also, in a mouse model of MOF, IFN beta was shown to be of benefit in protecting the alveolar structure from damage when compared to vehicle treated controls (Kiss et al. 2007). In addition, IFN beta treatment has been shown to prevent vascular leakage in ALI animal models. Enhanced adenosine production also inhibits leukocyte infiltration, thus reducing the escalation of inflammation and reperfusion

injury (Koszalka et al. 2004, Lennon et al. 1998 and Volmer et al. 2006). In a recent study, IFN beta-1a therapy was shown to reduce mortality in patients with ARDS by over 80 % (Bellingan et al. 2014). Pre-clinical data suggests that according the mechanism of action, FP-1201-lyo could also be protective in the reperfusion injury of the myocardium (Eckle et al. 2007), intestine (Hart et al. 2011) and kidneys (Grenz et al. 2008) and against SIRS induced by hypoxia (Eltzschig et al. 2012).

1.4 **Preclinical and clinical data**

Full details of preclinical and clinical information of FP-1201-lyo are found in the Investigator's Brochure.

2 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the safety and the efficacy of FP-1201-lyo over placebo on reducing all-cause mortality at study day 30; D30 (30 days from the first dose of study medication).

2.2 Secondary Objectives

1. To evaluate the efficacy of FP-1201-lyo treatment by assessing short term outcomes (D30) and mid-term outcomes D90 (3 months)
2. To evaluate the safety and tolerability of FP-1201-lyo treatment
3. To evaluate the pharmacodynamics (PD) of FP-1201-lyo
4. To evaluate the Tentative Disease Specific Marker CD73 and Potential Inflammatory Markers IL-6 and HGF
5. To evaluate neutralizing antibodies against IFN beta-1a (NAbs)

3 OVERALL DESIGN AND PLAN OF THE STUDY

3.1 Summary of Study Design

This is a multicentre, randomised, double-blind, Phase II, parallel group comparison study of the efficacy and safety of FP-1201-lyo compared to placebo in patients surviving emergency open surgery for an infra-renal ruptured abdominal aortic aneurysm. Both treatment groups will receive standard supportive care.

With an estimated screening failure rate of approximately 15%, maximum of 180 patients will be consented and entered into the study in order to randomise and initiate treatment of 152 patients. The sample size calculations will be re-evaluated after the first interim analysis has been performed.

The study design incorporates an Independent Data Monitoring Committee (IDMC) that will review safety data retrieved for interim analysis (i.e. Adverse Events [AE] and Serious Adverse Events [SAE]). Details of the IDMC are given in Section 9.8.

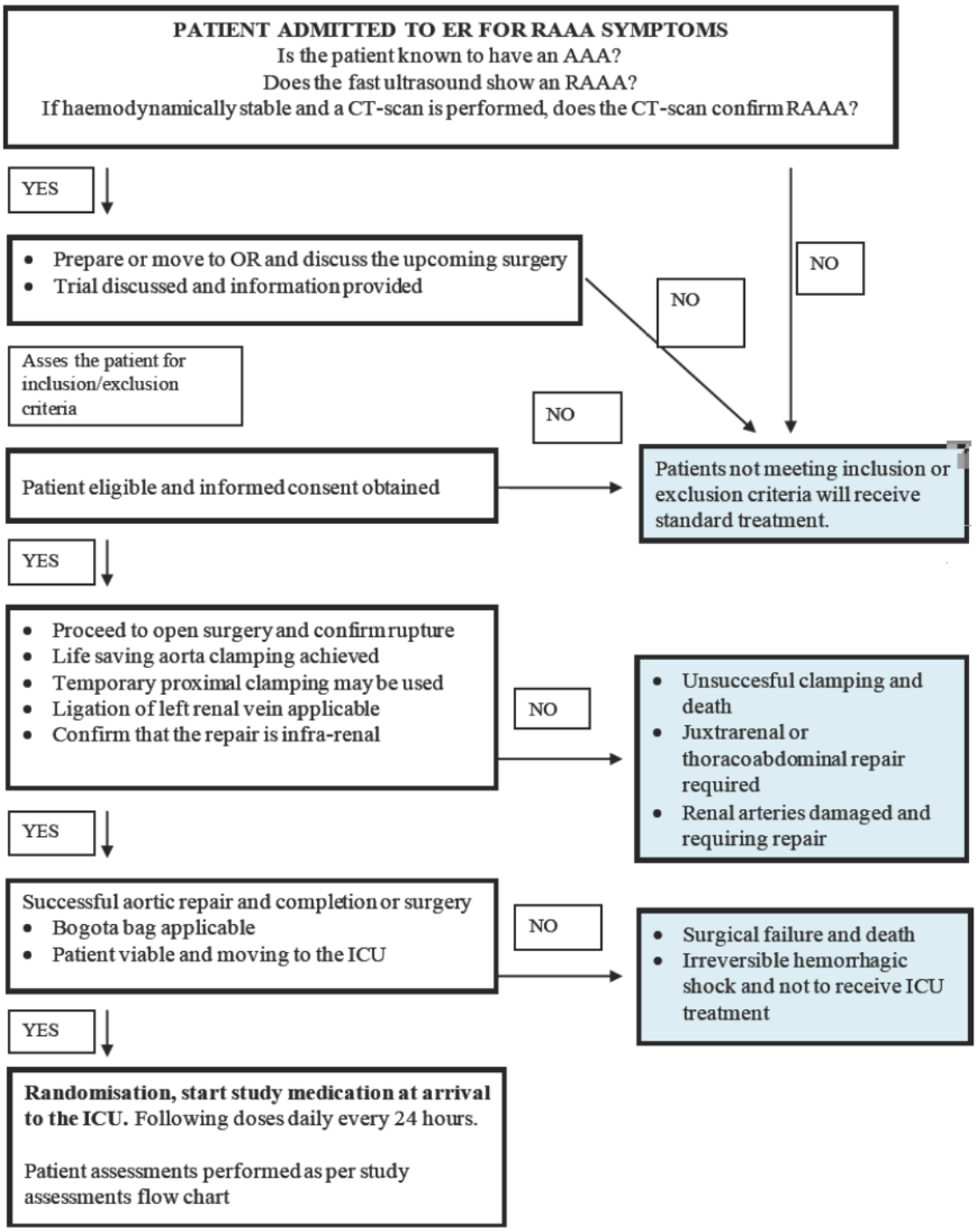
Patients will receive 10 µg FP-1201-lyo or placebo intravenously as a bolus injection once every 24 hours. The maximum duration of treatment will be 6 days. Treatment may be discontinued before 6 days if the patient's condition improves beyond the need for ICU treatment and if, in the opinion of the Investigator, the patient would likely not benefit from continuation of treatment.

A schedule for the tests and assessments to be conducted during this study is found in the Tables 5-8.

The study objectives and outcome measures to be used in this study are described in Sections 2 and 6.

The study design is summarised below in Figure 1.

Figure 1: Flow Diagram of Study Design



3.2 Criteria for the Study assessments

3.2.1 *Primary Efficacy Endpoint:*

- All-cause mortality at D30

Secondary Efficacy Endpoints:

- All-cause mortality at D90 (3 months)
- Number of ventilator free days (VFDs) at D30
- Number of days receiving hemodialysis at D30 and D90
- Number of organ failure free days up to D30 by means of the SOFA score
- Prevalence of abdominal compartment syndrome, i.e. intra-abdominal pressure (IAP) between study groups
- Neutralizing antibodies against IFN beta-1a (NAbs) in whole blood samples up to D30
- Disability at D90 (3 months) by modified ranking scale.

3.2.2 *Safety*

- Clinically significant treatment emergent adverse events (TEAEs) up to D30 from vital signs data, laboratory data, physical examinations and spontaneous reporting when conscious

3.2.3 *Pharmacoeconomics assessments*

- Length of ICU stay, in terms of ICU free days at D30
- Length of hospital stay, in terms of hospital free days at D90
- Length of stay at another health care facility at D90
- Length of hemodialysis needed
- Ventilation free days at D30

3.2.4 *Exploratory endpoints assessments*

Pharmacodynamics (PD):

- MxA (protein) concentration in whole blood samples from baseline up to D13.

Tentative Disease Specific Marker:

- CD73 concentration/activity in serum samples from baseline up to D13
- Potential Inflammatory Markers IL-6 and HGF in serum samples from baseline up to D13

3.3 Justification of the Study Design

This is a Phase II study to evaluate the efficacy and safety of FP-1201-lyo in the treatment of patients surviving open surgery for RAAA. The study is designed as a randomised, double-blind, placebo-controlled, parallel group, multi-centre clinical study.

Due to the randomisation procedure and the double-blind nature of this study the potential bias of the study results is minimised.

If there is any doubt regarding the integrity of the double-blind design, appropriate measures will be taken (refer to Section 5.4).

4 STUDY POPULATION

The study population will consist of patients undergoing emergency surgery for a ruptured abdominal aortic aneurysm. Patients must meet all the inclusion criteria and none of the exclusion criteria to be enrolled in the study. The inclusion and exclusion criteria apply during screening and prior to administration of the first dose of study drug on D0.

4.1 Inclusion Criteria

To be eligible for inclusion into this study, each patient must fulfil the following inclusion criteria (alternatively 1 or 2 and all 3, 4 and 5) during screening and prior to randomisation and the first dose of study medication being administered on D0:

1. Patients (male or female) presenting with a RAAA diagnosed by ultrasound or CT-scan in the emergency room
   - all forms of infrarenal RAAAs with or without coexisting iliac aneurysms are included

   or
2. Patients (male or female) presenting with symptoms of RAAA known to have an infrarenal AAA and proceeding straight to open repair without radiological assessment and rupture confirmed (retroperitoneal haematoma) intra-operatively

   and
3. Aneurysma repair must be infra-renal, i.e. the proximal anastomosis must be below the renal arteries and the renal arteries must stay intact. Temporary above the renal clamping can be used for a maximum of 30 minutes (total clamping time)

   and
4. Patients providing informed consent (written signed or witnessed)

   Or their next of kin providing written informed consent
5. Age over 18 years

4.2 Exclusion Criteria

To be eligible for inclusion into this study, each patient must not meet any of the following exclusion criteria **during screening or prior to randomisation and the first dose of study medication being administered:**

1. Moribund patient not eligible for treatment in ICU or expected to survive surgery
2. Markedly short life expectancy, e.g. advanced malignant disease
3. Current participation in another experimental treatment protocol
4. Significant congestive heart failure, defined as New York Heart Association (NYHA) class IV
5. Current treatment with IFN alpha or IFN beta

6. Dialysis therapy for chronic renal failure
7. Irreversible shock from haemorrhage
8. Unconsciousness when arriving to the hospital and during screening
9. rEVAR first (prior attempt for endovascular aortic repair for current rupture, prior elective EVAR applicable)
10. Earlier diagnosed cirrhosis in medical records
11. Pregnancy and women with child bearing potential without negative blood pregnancy test
12. Rupture not confirmed by CT or intra-operatively (impending ruptures are excluded)
13. RAAA requiring repair of the renal arteries or the proximal aorta
    - thoracoabdominal aneurysms requiring immediate repair
    - damaged renal arteries during emergency clamping requiring repair

    NOTE:
    - temporary clamping above the renal arteries (max 30 min total clamping time above the renal arteries) **does not** lead to exclusion
    - ligation of the left renal vein **does not** lead to exclusion

4.3 Confirmation of Patient Eligibility

To ensure appropriate enrolment into the study there will be a formal confirmation of eligibility process utilising the following procedure:

There will be an electronic Case Report Form (eCRF) checklist of inclusion and exclusion criteria; all items will need to be ticked correctly. The Clinical Data Management System (CDMS) will not allow a patient to progress to randomisation if these have been completed incorrectly. The vascular surgeon will perform this procedure and randomization immediately after the operation. If the ticks correspond to the inclusion criteria, the CDMS will make the patient available to be randomised.

If the ticks are against inclusion, the patient cannot be randomised and the reason for this will be noted in the eCRF, and the patient will be regarded as a screening failure.

With this method, only those patients whose data are recorded as meeting eligibility criteria can be randomised.

4.4 Patient Withdrawal and Replacement

4.4.1 *Discontinuation Criteria*

Patients may discontinue from the entire study, including follow-up, at any time without any reason and without prejudice to their future medical care; they are not obliged to state their reasons for withdrawing.

Additionally, the Investigator may discontinue a patient at any time if it is considered to be in the best interest of the patient. Discontinuation of study medication by the Investigator due to improvement of a patient's condition **does not** constitute a withdrawal as the patient will continue with the study assessments.

A patient **may be discontinued** from the study for example of the following reasons:

- Protocol violations including non-compliance with study procedures or patient lost to follow-up
- SAEs
- Administrative reasons
- Patient request
- Sponsor request
- Investigator request
- Authority request

In the case of a discontinuation, the Investigator must ensure that the status page in the eCRF for the **end of the study** is completed.

Patients may be required to **discontinue from study drug** after discussion with the Sponsor and/or Investigator for the following reasons:

- AEs
- At the discretion of the Investigator or if it is considered to be in the patient's best interest

If the administration of study medication is prematurely discontinued, the primary reason for discontinuation must be recorded in the appropriate section of the eCRF and all efforts made to complete the observations on that study treatment day as thoroughly as possible.

A complete final evaluation following the patient's discontinuation should be made on the day of the discontinuation/discharge, as described in Section 7.2. and any ongoing AEs should be followed up to resolution or study D30, whichever occurs first.

The study will be terminated if, in the opinion of the Sponsor, significant safety concerns arise during the conduct of the study.

Patients who discontinue study drug may continue in the study. The Investigator must ensure that the status page in the eCRF for the end of study is completed.

In all cases, the reason(s) for discontinuation, including the primary reason, must be recorded in the eCRF. If a patient prematurely discontinue from the study drug for any reason, the Investigator must make every effort to perform the evaluations described for the follow-up visits. Any on-going AEs should be followed up to resolution or D30 whichever is the sooner. See also Section 7.6.1. A permission will be sought to access the patient's medical records for data relevant to the study (e.g., mortality, VFDs, etc.) to complete the D30 and D90 follow up. See also section 9.6.2.

Patients who withdraw consent for their data to be analysed will be identified in the CDMS. Any data collected will not be deleted, but will not be used in any subsequent outputs.

Patients that have received at least one dose of the study drug and discontinued will not be replaced.

The study will be terminated if, in the opinion of the IDMC or the Sponsor, significant safety concerns arise during the conduct of the study.

4.4.1.1 Non-attendance of Follow-up Assessments

Attempts should be made to contact patients discharged from hospital who do not attend their study follow-up assessments to ensure their well-being. In such cases, the

patient will be contacted at least twice by telephone and once by letter to request that they attend the scheduled follow-up assessment. If patients do not respond they will be considered as *lost to follow up* at that time point. If a patient is lost to follow-up, wherever possible mortality data will be sought at all remaining mortality time points from alternative sources such as the patient's local physician.

4.4.2 *Replacement Policy*

All patients who become ineligible after consenting but before randomisation are replaced and deemed as screening failures. A screening failure is defined as any patient who does not comply with the inclusion and exclusion criteria during screening **or** prior to randomisation and receiving the first dose of study medication.

Patients who complete screening and are randomised and receive at least 1 dose of the study medication will not be replaced even if later withdrawn or lost to follow up.

4.5 Planned Sample Size and Number of Study Centres

It is planned to randomise 152 patients at 10-18 hospital study centres in Finland, in UK, in Lithuania and in Estonia and possibly in other countries in EEA and in USA for this study. Possible additional selection will be decided later, as required. See Section 8.2. for a discussion of sample size.

4.6 Patient Randomisation

4.6.1 *Randomisation Scheme*

Patients are randomly assigned to treatment with FP-1201-lyo or placebo in the randomisation ratio of 2:1 (active:placebo) for treatment groups, stratified by sex and age.

The treatment assigned to each patient is determined according to a computer-generated randomisation list within eCRF.

4.6.2 *Randomisation of Patients to Treatment*

Randomisation of patients to treatment will occur immediately after completion of surgery and after all screening procedures have been performed and eligibility for inclusion in the study has been confirmed. Each randomised patient will receive a unique randomisation number. Randomised patients who terminate their study participation for any reason, regardless of whether study drug was taken or not, will retain their randomisation number.

The Investigator will use IWRS for randomisation of patients. Details can be found in the study file.

5 STUDY DRUG

5.1 Identity

RentschlerBiopharma SE, Laupheim, Germany manufactures lyophilised FP-1201-lyo (recombinant human IFN beta-1a) and the matched placebo. Both FP-1201-lyo and placebo powders are free of animal serum and human serum albumin. Vetter Pharma International Services, Ravensburg, Germany manufactures pre-filled water for injection (WFI) diluent syringes.

A MixJect® transfer device will be used in this study. This MixJect® transfer device is a single unit for reconstituting a powdered drug with a diluent pre-filled syringe. Upon reconstitution, the drug is available for immediate injection. The MixJect® transfer device enables the safe, rapid and easy preparation of lyophilised drugs. The MixJect® transfer device is manufactured by West Pharmaceutical Services GmbH, Germany/Ra'anana, Israel. The device carries the CE mark and has 510(k) approval by the United States Food and Drug Administration.

PCI, UK, is responsible for the packaging of FP-1201-lyo and matched placebo in a carton box. The pre-filled WFI diluent syringe, the MixJect® transfer device and the reconstitution instructions are packaged in the accessorial carton kit. PCI, UK or Ireland, is responsible for distributing the investigational medicinal product to the study sites.

5.2 Administration

FP-1201-lyo 10 µg (or placebo) will be diluted in WFI near the patient/in the ICU. Once prepared, the dose must be administered to the patient immediately. The diluted FP-1201-lyo or placebo will be administered as an intravenous bolus injection via a central or peripheral line. The injection will be followed with a 5 mL flush of sterile saline (not provided).

Study drug injections will be given once daily for 6 days. The injection should be given at the same time each day ±1 hour providing the patient's condition allows this. If for any reason this is not possible, the treatment window may be extended by up to 4 hours i.e. ±2 hours. The reason for the delay must be entered in the eCRF. Subsequent doses should not be delayed and should revert to the original time schedule (e.g., if the D1 dose was at 13:00, the D2 dose was delayed and given at 15:00, the D3 dose should be given at 13:00 ±1 hour).

No dose modifications or temporary cessations of study drug administration are allowed. If a delay beyond the 4-hour window described above is required, the patient must be withdrawn from study drug but all data must continue to be collected per protocol. Administration of a second course of study drug is not permitted.

The first dose of study medication is administered when the patient has arrived at the ICU after successful infra-renal aortic repair with intact renal arteries given the patient is viable. A prior temporary proximal aortic clamp (total maximum clamping time of 30 min) may be used to asses and control the operative situation. Surgical re-inventions (e.g. bleeding, lower limb embolia, intra-abdominal pressure and open abdomen, bowel resection) do not lead to exclusion if the study drug is administered as scheduled and the re-interventions do not violate the inclusion criteria, i.e. re-doing the upper anastomosis to the renal arteries or above.

5.3 Packaging, Labelling and Storage

Study drug, i.e. FP-1201-lyo or matched placebo, is packaged in a carton. The pre-filled WFI diluent syringe and the MixJect® transfer device are packaged in an accessorial carton kit.

Six investigational medicinal products and six accessorial carton kits are reserved for each patient to cover the 6-day treatment period.

Labelling will be prepared by PCI to meet the local regulatory requirements.

All study drug supplies must be stored in accordance with the manufacturer's instructions, i.e., FP-1201-lyo/placebo is to be stored at 2 8°C and the accessorial carton kits are to be stored at room temperature. Until dispensed to the patients, the study drug will be stored in a securely locked area, accessible to authorised personnel only.

The investigational medicinal product and the accessorial carton kits are dispensed only by the Investigator or by a member of staff specifically authorised by the Investigator, or by a pharmacist, as appropriate.

5.4 Blinding and Breaking the Blind

The study will be performed in a double-blind manner. All study drugs will be supplied in identical vials and will be similar in colour and appearance, thereby enabling double-blind conditions.

The treating physician (investigator) is responsible for the medical care of the trial patient and the study set up allows the investigator to rapidly break the treatment code in case of an emergency.

The study blind should only be broken in a medical emergency (where knowledge of the study drug received would affect the treatment of the emergency) or as a regulatory requirement (e.g., for SAEs or death). Note that there is no specific antidote or method of removing the study drug from the body (such as dialysis) and the best available care for the patient should be continued.

If the blind is broken, the date, time and reason must be recorded in the patient's eCRF and any associated AE report. It is the responsibility of the investigator to promptly document and explain any unblinding to the sponsor/CRO.

Detailed instructions for the use of the IWRS in order to break the study blind for a patient are provided in a separate document that will be filed in the Site File and Trial Master File. As well as the IWRS, a backup system enabling unblinding of treatment is provided to the sites.

After a patient has been unblinded data collection should continue as per protocol.

Suspected unexpected serious adverse reactions (SUSARs), which are subject to expedited reporting, should be unblinded before submission to the regulatory authorities and Independent Ethics Committees (IECs).

The overall randomisation code will be broken only for reporting purposes (for interim and final analyses). This will occur once all D90 clinical data have been entered into the database and all data queries have been resolved, and the assignment of patients to the analysis sets has been completed. The randomisation code will be opened for the interim analysis, which is performed when at least 31 patients have been enrolled and the D30 clinical data is available.

5.5 Drug Accountability

The Investigator is responsible for maintaining accurate study drug accountability records throughout the study.

Each dispensing of study drug will be documented in the eCRF.

The Investigator is responsible for ensuring all unused medication is destroyed at the investigational site following the appropriate drug accountability procedures.

5.6 Compliance

The study drug is administered intravenously at the study site, so it is not necessary to monitor patient compliance with the study drug regimen.

5.7 Previous and Concomitant Medications

Concomitant medication or therapy which is considered necessary for the patient's welfare and which will not interfere with the study medication, may be given at the discretion of the Investigator. There are no prohibited medications in this study.

Concomitant medications and therapies will be recorded from screening to D30. Administration of all concomitant drugs and therapies must be reported in the appropriate section of the eCRF along with the minimum and maximum dose levels administered (if applicable). Recording of dates of administration/therapy for chronic treatment and actual dates of administration of all acute concomitant medication is required.

Additionally, section 5.8 provides guidelines for concomitant medications to be administered for certain medically-expected AEs for this particular study population.

If a patient is discharged from the hospital prior to D30, the patient must be instructed that the Investigator should be informed about additional medication up to D30.

Patients in this study will be managed with supportive care measures according to the best clinical practice established locally in each ICU.

5.8 Guidance on medications to be administered/patient management for expected Adverse Events

Recombinant Human IFN beta-1a has been widely used in man for the treatment of multiple sclerosis and is considered safe. Some adverse effects are anticipated. Most common are changes in blood biochemistry of liver function, i.e. ALAT, ASAT, AFOS. A slight elevation in liver enzymes is often seen, and needs to be followed. These changes usually subside after cessation of treatment. Most common severe adverse effects are fever, tachycardia and rigor, since the drug substance is to some extent pyrogenic by nature. These adverse effects mostly occur shortly after administration and cease after treatment. These adverse effects may be managed with otherwise suitable medication depending on the symptom: paracetamol or other antipyretics for fever, beta blockers for tachycardia, benzodiazepines for rigor or even propofol sedation in the ICU setting.

Few adverse effects are expected after the treatment period since, as shown in the FPCLI001 study, FP-1201 activity decreases significantly within few days after administration, according to MxA measurements. Thus, the IMP will be washed out before discharge from the hospital. For more information on the anticipated effects of the FP-1201-lyo treatment see the **Investigators' Brochure**.

6 VARIABLES AND METHODS OF ASSESSMENT

The timing of the assessments of the variables is shown in the Schedule of Procedures (Tables 5, 6 and 7).

6.1 Efficacy Variables

The following efficacy variables will be assessed:

- Mortality assessments
- Ventilator free days (VFDs)
- ICU free days
- Organ failure free days
- Days in hospital and/or other health care facility
- Days on haemodialysis
- Prevalence of abdominal compartment syndrome as measured by intra-abdominal pressure (IAP)

6.2 Methods and Timing for Assessing, Recording and Analysing Efficacy Parameters

6.2.1 *Mortality assessments*

The following mortality assessments are to be conducted:

- All-cause mortality at D30 and D90 (3 months)
- Kaplan-Meier survival curve to D90

Mortality is to be captured by assessing whether the patient is alive or dead and by recording the date of death and reason/diagnosis leading to death when available.

6.2.2 *Disability assessment*

Modified ranking scale (mRS) at D0 and D90 will be used to evaluate study subject disability. Single mRS value is applied for every patient based on patient or caregiver interview (Table 9). Pre-operation D0 mRS value is collected for reference (possible to collect also retrospectively by interview).

6.2.3 *Ventilator free days (VFDs)*

The number of VFDs at D30 will be assessed.

Definition of VFDs to D30:

VFDs to D30 is defined as the number of calendar days after initiating unassisted breathing (UAB) to D30 from first treatment, assuming a patient survives at least 48 consecutive hours after initiating UAB.

For example: If a patient initiates UAB on D16 and survives to D30, that patient would be assigned a VFD value of 14. If a patient initiates UAB on D16 but dies on D25 he/she would be assigned a VFD value of 9. If a patient survives for more than 48 hours after initiating UAB but then requires assisted breathing (for any reason) before D30 then the VFD value would be the total number of UAB days before D30 unless a period of assisted breathing was less than 24 hours and the purpose of

assisted breathing was a surgical procedure. Patients who die without initiating UAB will be assigned a VFD value of zero. All patients, whether still on or already off positive pressure ventilation, who are transferred to another hospital or healthcare facility prior to D30, will be followed up to assess the VFD outcome at D30.

Patients transferred to other health care facilities or to another hospital prior to D30 while still receiving assisted breathing/without assisted breathing will be followed until D30 to assess this efficacy measure. Unassisted breathing (UAB) is defined as any of the following:

- spontaneous breathing with face mask
- nasal prong oxygen or room air
- t-tube breathing
- tracheostomy mask breathing
- CPAP < 5 without pressure support (PS) or IMV assistance
- use of CPAP or BIPAP solely for sleep apnoea management

6.2.4 *ICU free days*

The number of ICU free days will be assessed at D30.

Definition of ICU free days:

ICU free days are defined as the number of days from the time of ICU discharge to D30 after the first dose of study medication, assuming survival for at least two consecutive calendar days after ICU discharge and continued stay outside the ICU setting to D30. If a patient returns to the ICU and subsequently needs ICU admission to D30, ICU free days will be counted from the end of the last period of ICU discharge to D30. A period of ICU admission lasting less than 24 hours in relation to a surgical procedure is considered an ICU free day. If a patient is held at the ICU at D29 or dies at the ICU prior to D30, ICU free days will be zero. Patients transferred to another hospital or other health care facility will be followed until D30 to assess this endpoint.

6.2.5 *Organ failure free days*

Organ failure free days are assessed at D30.

Definition of organ failure free days:

Organ failure free days are defined as the number of days in the first 30 days after the first dose of study medication that the patient is alive and free of organ failure with a SOFA score of zero for the following six organ parameters: respiration, coagulation, liver, cardiovascular, CNS and renal function (refer to the SOFA score illustrated in Table 1).

The total SOFA score and the individual elements of the SOFA score are assessed daily from baseline to D30 if the patient is in the ICU and have an arterial catheter (or is on the ward but have an arterial catheter suitable for PaO_2/FiO_2 assessment), include:

a) PaO_2/FiO_2 (mmHg)

b) platelets $\times 10^3/mm^3$

c) bilirubin (mg/dl)

d) hypotension

e) GCS (an estimation will be used for sedated patients)

f) creatinine (mg/dl)

Refer to Table 8 for the SOFA assessment schedules.

Patients who die without achieving a SOFA score of zero will be assigned an organ failure free days value of zero.

Table 1: The SOFA score

SOFA score	0	1	2	3	4
Respiration					
PaO_2/FiO_2, mmHg	>400	>300 ≤400	>200 ≤300	>100 ≤200 with respiration support	≤100
Coagulation					
Platelets × $10^3/\mu l$	>150	>100 ≤150	>50 ≤100	>20 ≤50	≤20
Liver					
Bilirubin, mg/dl	<1.2	≥1.2 <2.0	≥2.0 <6.0	≥6.0 <12.0	≥12.0
(µmol/Ll)	(<20)	(≥20 <33)	(≥33 <102)	(≥102 <204)	(≥204)
Cardiovascular					
Hypotension[a]	No hypo tension	MAP <70 mmHg	Dopamine ≤5 or dobutamine (any dose)	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central nervous system					
Glasgow Coma Scale[b, c]	15	13 14	10 12	6 9	<6
Renal					
Creatinine, mg/dl	<1.2	≥1.2 <2.0	≥2.0 <3.5	≥3.5 <5.0	≥5.0
or µmol/l or urine output	<110	≥110 <171	≥171 <300	≥300 <440 or <500 mL/d	≥440 or <200 mL/d

[a] *Adrenergic agents administered for at least 1 hour (doses are given in µg/kg/min).*

[b] *For patients who are intubated, the verbal response is scored as:*

5 – Seems able to talk

3 – Questionable ability to talk

1 – Generally unresponsive.

[c] *For patients who are sedated use an estimated score for GCS (the assumption is 15, if no other factors than sedation affect GCS)*

Abbreviations: MAP=mean arterial pressure; PaO_2/FiO_2=partial pressure of oxygen/fraction of inspired oxygen; SOFA=Sequential Organ Failure Assessment.

6.2.6 *Days in hospital and/or other health care unit*

The length of a patient's hospital stay will be assessed by:

- the number of days the patient stayed in hospital at D30 and D90
- the number of days the patient stayed at another primary or rehabilitating health care unit after hospital discharge at D30 and D90.

6.2.7 *Days on haemodialysis*

The number of days on haemodialysis will be assessed at D30 and D90. Haemodialysis at D90 is considered permanent.

6.2.8 *Prevalence of compartment syndrome as measured by intra-abdominal pressure (IAP)*

Intra-abdominal pressure (IAP) is routinely measured during ICU stay via urine bladder catheter. IAP is recorded daily and a comparison of IAP between study groups is made.

6.3 Safety Variables

6.3.1 *Adverse Events*

6.3.1.1 Collection of Adverse Events

It is the responsibility of the Investigator to collect all AEs (both serious and non-serious) derived by observation, by spontaneous unsolicited reports of patients, and, where appropriate, by routine open questioning, e.g., "How have you felt since I last saw you?"

6.3.1.2 Definitions

Definitions of AEs and SAEs and their documentation and reporting within this study follow International Conference on Harmonisation (ICH) Good Clinical Practice, European Union, and national regulations and requirements (Clinical safety data management 1994).

An AE is defined as any untoward medical occurrence that occurs in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An 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 product, whether or not it is considered related to the product.

All AEs up to D30 are collected. All AEs up to D30, which lead to death, are reported as SAEs. However, all deaths up to D90 will be reported as SAEs. Concomitant illnesses, which existed before entry into the study, will not be considered AEs unless there is any deterioration from baseline that is considered clinically relevant or significant during treatment or follow-up period until D30 or discharge from ICU. All AEs must be documented, regardless of the source of identification (e.g., physical examination, laboratory assessment, ECG, reported by patient).

Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page.

A TEAE is defined as an AE that begins or that worsens in severity after at least one dose of study drug has been administered up to D30.

See 6.3.1.4 for the schedule of collection of adverse events

6.3.1.3 Assessment of Adverse Events

It is recognised that the patient population in the ICU will experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of their underlying disease and the impact of standard therapies. These will not necessarily constitute an AE unless they require significant intervention, lead to discontinuation of blinded study drug or are considered to be of concern in the Investigator's clinical judgement.

Each AE will be assessed by the Investigator with regard to the following categories:

6.3.1.3.1 Seriousness

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening. This means that the patient is at risk of death at the time of the event. It does not mean that the event hypothetically might have caused death if it were more severe
- 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 that may not be immediately life-threatening or result in death or hospitalisation but that may jeopardise the patient or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse

"At any dose" does not imply that the patient is receiving study treatment at the time of the event. Study drug doses may have been given during treatment cycles or interrupted temporarily prior to the onset of the SAE, but may have contributed to the event.

6.3.1.3.2 Intensity

Classical reporting of mild, moderate and severe AEs making a reference to the patient's functional status is difficult for a randomised study in critically ill patients. Patients enrolled in this study will primarily be mechanically ventilated and comatose due to their underlying condition and/or the drugs they are prescribed for sedation and analgesia in the ICU. Therefore, the classical approach to AE reporting, which requires patient communication and evaluation of the impact on functioning will be adapted to the ICU environment. The Investigator will be responsible for the assessment of severity, using the categories of mild, moderate or severe to describe each AE as:

- **Mild:** Does not interfere with patient's usual function
- **Moderate:** Interferes to some extent with patient's usual function
- **Severe:** Interferes significantly with patient's usual function

Note the distinction between serious and severe AEs. **Severe** is a measure of intensity whereas an event must meet one of the criteria for serious events listed in Section 6.2.1.3.1 to be considered **serious**; thus, a **severe** reaction is not necessarily a

serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed in Section 6.2.1.3.1.

6.3.1.3.3 Causality

The Investigator will assess the causality/relationship between the study drug and the AE and record that assessment in the eCRF. Causality will be assessed as:

- **Not related:** AE is obviously explained by another cause*; or* the time of occurrence of AE is not reasonably related to administration of the study drug
- **Possibly related:** Study drug administration and AE occurrence are reasonably related in time*; and* AE is explained equally well by causes other than study drug
- **Probably related:** Study drug administration and the occurrence of the AE are reasonably related in time*; and* the AE is more likely explained by exposure to study drug than by other mechanisms

The most likely cause of an AE (e.g., disease under treatment, concomitant disease, concomitant medication, other) will be indicated in the eCRF with details of the concomitant disease or medication or other cause.

6.3.1.3.4 Clinical Laboratory Adverse Event

Abnormal laboratory findings (e.g., biochemistry, haematology, urinalysis) or other abnormal assessments (e.g., vital signs) that are judged by the Investigator as clinically significant will, if certain requirements are met, be recorded as AEs or SAEs. Clinically significant abnormal laboratory findings or other abnormal assessments that meet the definition of an AE or SAE and are detected during the study, or are present at baseline and significantly worsen following the start of the study, will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied (unless judged by the Investigator as more severe than expected for the patient's condition), or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The Investigator will exercise their medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

6.3.1.4 Recording Adverse Events

AE reporting will extend from signing of informed consent. AEs occurring after D30 should be reported to the Sponsor by the Investigator if the Investigator considers there is a causal relationship with the study drug. However, all deaths will be recorded and reported as SAEs throughout the study (up until D90).

All AE reports should contain a brief description of the event, date and time of onset, date and time of resolution, intensity, treatment required, relationship to study drug, action taken with the study drug, outcome, and whether the event is classified as serious.

Recording a diagnosis (when possible) is preferred to record a list of associated signs and symptoms. However, if a diagnosis is known but there are associated signs or symptoms not generally attributed to the diagnosis, the diagnosis and each sign or symptom must be recorded separately.

6.3.1.5 Reporting Serious Adverse Events

According to applicable European Union regulations and requirements, an SAE must be reported to the Sponsor from the trial site as soon as possible **within 24 hours** of becoming aware of the SAE. A medically qualified person at the trial site identified on the Delegation of Authority Log with this responsibility must assess the SAE. Any member of the clinical trial site staff can assist in reporting an initial SAE. The Principal Investigator or delegated sub-investigators are responsible for the SAE reporting procedures at the site during the trial, and must always sign-off on each SAE even if other site staff have reported the event on behalf of the investigators. A delegation log at each trial site will clearly show delegation of responsibilities regarding SAE reporting.

The SAE form must be completed with all the relevant information and forwarded to Crown Pharmacovigilance by:

- Email: [redacted]

  or

- Fax: [redacted] In case of delivery failure, please **call:** [redacted]

If the SAE is urgently reported by telephone, a paper SAE form must always be completed and forwarded to Crown Pharmacovigilance as soon as possible.

The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE report and the seriousness and the causal relationship of the event to study treatment will be evaluated. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the reference document (Investigator Brochure). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.

If consensus on the assessment cannot be reached between the parties (e.g., Investigator and Sponsor/Sponsor's delegate), all opinions will be provided in the Council for International Organizations of Medical Sciences Form I report and reporting to the CA and IEC should be based on the highest degree of causality provided.

Details for reporting SUSARs can be found in Section 6.3.1.7.

All SAEs will be recorded that occur between signing of informed consent and D30. Events occurring after D30 and coming to the attention of the Investigator should be reported only if they are considered in the opinion of the Investigator to be causally related to the investigational drug. However, all deaths up to D90 will be reported as SAEs.

All SAEs occurring as described above, must be reported **within 24 hours** by email or fax to Crown Pharmacovigilance.

The minimum information required for an initial report is:

- Details of person sending the report (i.e., name and address of Investigator)
- Patient identification details (screening/randomisation number, age, sex, NOT patient name)
- Protocol number
- Description of SAE
- Causality assessment

However, all points on the SAE form should be covered in the initial report and the completed SAE form itself must be emailed or faxed to Crown Pharmacovigilance.

After receipt of the initial report, Crown Pharmacovigilance will review the information and, if necessary, contact the Investigator to obtain further information for assessment of the event. Crown CRO will be responsible for all information processing and reporting according to local legal requirements.

Detailed instructions concerning SAE reporting procedures will be described in a Safety Management Plan written by Crown Pharmacovigilance. SAE Report Form and contact information for reporting SAEs will be provided to the sites.

6.3.1.6 Follow-up of Adverse Events

All AEs experienced by a patient, irrespective of the suspected causality, will be monitored until: the AE has resolved; any abnormal laboratory values have returned to baseline or stabilised at a level acceptable to the Investigator and Medical Monitor; there is a satisfactory explanation for the changes observed; the patient is lost to follow-up; or the patient has died.

6.3.1.7 Suspected Unexpected Serious Adverse Reactions

Any AE that is serious, associated with the use of the study drug, and unexpected (SUSAR) has additional reporting requirements, as described below.

- If the SUSAR is fatal or life threatening, associated with use of the study drug and unexpected, regulatory authorities and IECs must be notified **within 7 calendar days** after the Sponsor learns of the event. Additional follow-up information (cause of death, autopsy report and hospital report) should be reported **within an additional 8 days** (15 days total).
- If the SUSAR is not fatal or life threatening but is otherwise serious, associated with the use of the study drug and unexpected, regulatory authorities and IECs must be notified **within 15 calendar days** after the Sponsor learns of the event.

The Sponsor will notify the Investigators in a timely fashion of relevant information about SUSARs that could adversely affect the safety of patients. Follow-up information may be submitted if necessary.

The Sponsor will also provide annual safety updates to the regulatory authorities and IECs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.

6.3.1.8 Pregnancy

Monitoring of pregnancies is not applicable to this study because pregnancy is an exclusion criterion and a pregnancy test is performed in all women of childbearing potential at screening. Owing to the nature of the study involving short (6-day) treatment with the study drug in an ICU setting, it is not possible for women to become pregnant during treatment and for there to be any foetal exposure to the study drug.

6.3.2 ***Laboratory Variables***

The biochemistry and haematology analysis will be performed at the hospital laboratories of the individual Investigator sites. These analyses are mostly included in the standard care of RAAA patients. Copies of laboratory accreditation and relevant

reference ranges will be provided to the Sponsor or representative prior to the analysis of the first patient sample at that site.

The laboratory variables measured in the study will be as detailed in Table 2.

Blood samples for determination of biochemistry and haematology will be taken at pre-dose on D0 (baseline value), D1, D2, D3, D4, D5, D6, D9, D13 and D30 (or on a particular date if a patient is discharged from initial operating hospital or discontinues from the study after D6 but prior to D30), as detailed in the study flow charts in Tables 5 & 6. Patient is not invited to laboratory visit, once discharged from hospital, except on D30 for assessment of NAbs. The date and time of collection will be recorded in the eCRF.

Table 2: Laboratory Variables

Biochemistry	**Haematology** *Includes coagulation*	**Other**
Alanine transaminase (ALAT) Alkaline phosphatase (AFOS) Aspartate transaminase (ASAT) Bicarbonate Lactate pH Bilirubin Calcium Creatinine Potassium Sodium (blood gas value acceptable)	Haemoglobin Leucocyte differential count (absolute) Mean cell volume Platelet count Red cell count White cell count	Pregnancy test

Total volume of blood required for biochemistry and haematology samples per patient are shown below in Table 3.

Table 3: Total Volume of Blood required for Biochemistry/Haematology Samples

Assessment	**Number of Samples**	**Per Sample Volume (mL)**	**Total Volume (mL)**
Biochemistry	9	6	**56**
Haematology	9	9	**81**
Pregnancy test	1	4	**4**
			141

6.3.3 *Vital Signs*

Vital signs are recorded at D0 pre-dose (baseline) and continuously during ICU stay, and at least daily during hospital care. Reporting points D0 pre-dose (0 hrs), D1, D2, D3, D4, D5, D6, D9, D13 and D30 (or on a particular date if a patient withdraws from the study after D6 but prior to D30), as detailed in the study flow charts. The date and time of collection of each parameter will be recorded in the eCRF.

Vital sign variables include:

- Blood pressure (BP) (mmHg): to be recorded intra-arterially or using a device with an appropriate cuff size for the patient.
- Heart rate (HR) (bpm): measured as per clinical practice on each ICU
- Temperature (C°): auricular (preferred, but other clinically used routine methods are also acceptable) temperature

6.3.4 *Physical examination*

A physical examination covering the major organ systems will be performed at screening (baseline) and D30 (or when a patient is discharged from the hospital prior to D30).

At screening the physical examination also includes:

- predicted body weight if actual weight is not attainable. Patient reported weight is acceptable. Calculate the predicted body weight (kg) using the following formulae:
  i. ♂ 50 + 0.91(height in cm 152.4)
  ii. ♀ 45.5+0.91(height in cm 152.4)
- actual height (in cm) reported by patient

6.4 Baseline characteristics and disposition

As per Study Flow Chart baseline assessments consist of those assessments carried out after the informed consent has been obtained in the screening period and those carried out prior to the first dose of study medication on D0. Peri procedural information is collected as it may have impact on the patient outcomes. These include duration of the surgical procedure for RAAA, total clamping time, total bleeding volume, total volume substitution, total blood substitution, total red blood cells substitution, total platelets substitution, total crystalloids substitution and total diuresis volume during procedure. Recycling of blood during surgery (yes/no).

Demographic and baseline characteristics are summarised by treatment group and overall. Statistical comparisons are undertaken to compare treatment groups for any of these parameters.

Disposition and reasons for discontinuation are summarised for all patients together with treatment exposure and study duration by treatment group.

6.5 Pharmacoeconomic Evaluation

To calculate the expected incremental cost effectiveness of intravenous FP-1201-lyo compared with standard care in the treatment of patients with RAAA and performed open aortic repair, the following parameters will be measured/collected:

- AEs between the first dose of study medication at D0 0 pre-dose and D30

- concomitant medications and therapies as recorded from Screening to D30
- the number of days in ICU from D0 pre-dose to D30
- the number of days in hospital from D0 pre-dose to D90 (3 months)
- the number of days at another health care facility from D0 pre-dose to D90
- the number of days on haemodialysis from Screening to D30 and D90
- the number of organ failure free days from D0 pre-dose to D30
- the number of VFDs from D0 pre-dose to D30

6.6 Exploratory Variables

6.6.1 *Methods and Timing for Assessing, Recording and Analysing Pharmacodynamic Parameters*

Blood samples for the NAbs assessments are collected at D0 pre-dose (baseline) and at D30. Blood samples for the MxA, Tentative Disease Specific Marker (CD73) and Potential Inflammatory Markers (IL-6 and HGF) assessments are collected at D0 pre-dose (baseline), at D1, D2, D3, D4, D5, D6, D9 and D13 assuming the patient is hospitalized as detailed in the study flow charts in Tables 5 and 6.

MxA, CD73, NAbs and PIM blood sample preparation and sample storage details are provided in the study specific Laboratory Manual. It is essential that the actual time and date of collection of each PD sample be recorded in the sample collection form provided with the laboratory kits.

MxA, CD73 and NAbs samples are analysed centrally by [redacted], and PIMs in [redacted].

The total volume of blood required for samples per patient is shown below in Table 4.

Table 4 Total Volume of Blood required for MxA, CD73 and PIMs

PD Parameter	Number of Samples	Per Sample Volume (mL)	Total Volume (mL)
CD73	9	2.5	**22.5**
MxA	9	2	**18**
PIM	9	2.5	**22.5**
NAbs	2	2.5	**5**

7 STUDY CONDUCT

For the purposes of this study, study day 0 (D0) is defined as the day of surgery and the first day of treatment with FP-1201-lyo or placebo. All days thereafter are defined as "Dn", denoting the number of postoperative days (e.g. D1, D2 etc.) until D30. A follow-up assessment regarding the final outcome at D90 (3 months) is carried out using patient files or phone. For NAbs assessment on D30 patient is invited for a laboratory visit (D30 ± 5 days).

Baseline assessments consist of those carried out in the screening period and those prior to the first dose of study medication on D0.

The study consists of the following study periods and tests and evaluation time points:

- **Baseline period:** Screening and study day 0 (D0) pre-dose
- **Treatment period:** D0 0 hrs to D5 (i.e., D0, D1, D2, D3, D4, and D5)
- **Short term follow-up period:** D6 to D30 daily if patient still hospitalized
- **Mid-term (final) follow-up:** D90 (3 months) through patient charts and registers and by phone.

For patients whose conditions have improved to the point where they are discharged from the ICU and the Investigator decides not to continue study treatment, the study assessments schedule should be followed. If an improving patient is discharged from the ICU during the treatment period then the patient will be followed daily during hospitalisation (in the operating hospital), and after a possible hospital discharge at D30.

A schedule for the tests and evaluations to be conducted in this study is found in the flow charts. Details on the timing of each assessment on a given study day is given in the flow charts.

The expected duration of the study for each patient is 1 month plus a patient records based follow up at 3 months.

7.1 Study Procedures Flow Charts

Table 5: Flow Chart for Baseline and Treatment Periods

ASSESSMENTS	Baseline Period		Treatment Period*					
	Screen	D0	D0	D1	D2	D3	D4	D5
	Enrolment	pre-dose	ICU					
Symptoms, d agnos s and treatment of RAAA	X							
Med ca H story	X							
Inc us on / Exc us on Cr ter a	X							
Conf rmat on of a e g b ty cr ter a		X						
Informed Consent +	X							
Demography	X							
Phys ca Exam (nc . PB, pu se)	X							
T me of onset of symptoms	X							

Hemodynam c co apse before ER	X							
Date and t me of entry to ER	X							
Mov ng to OR for open repa r	X							
Pat ent Random sat on (after consent & e g b ty cr ter a conf rmed)		X						
Hemodynam c co apse before c amp ng (yes/no)		X						
Prox ma aort c c amp used(m nutes/no)		X						
Check that rena arter es are ntact		X						
Check that RAAA s nfrarena		X						
Check that the pat ent s st sa vageab e, no rrevers b e shock		X	X					
mRS ++		X						
SOFA Scor ng ❖ (the worst obta ned da y va ue shou d be used)			X	X	X	X	X	X
Vent ator Free Days (VFDs)			X	X	X	X	X	X
V ta S gns; Temp, BP, HR (morn ng va ue c osest to 8am)		X		X	X	X	X	X
B ood B ochem stry (morn ng ab round)		X		X	X	X	X	X
Haemato ogy (morn ng ab round)		X		X	X	X	X	X
Pregnancy test **		X						
Intra abdom na pressure (IAP) morn ng va ue c osest to 8 am				X	X	X	X	X
FP-1201-lyo or placebo administration∇			**Dose1**	**Dose 2**	**Dose 3**	**Dose 4**	**Dose 5**	**Dose 6**
MxA, CD73 and PIM		X 1h pre dose		X 22h ±2h s nce Dose1, but before Dose 2	X 22h ±2h s nce Dose2, but before Dose 3	X 22h ±2h s nce Dose3, but before Dose 4	X 22h ±2h s nce Dose4, but before Dose 5	X 22h ±2h s nce Dose5, but before Dose 6
NAbs		X						
Concom tant Med cat ons/Therap es	X	X	X	X	X	X	X	X
AE Record ng (after obta ned consent)		X	X	X	X	X	X	X
Major surg ca outcome record ng			X	X	X	X	X	X
Assessment of morta ty and reason/d agnos s of death	X	X	X	X	X	X	X	X

KEY:

* Assessments prior to D30 are only performed if patient is still hospitalised in the same hospital initially operated. If the patient is moved to a different hospital, assessments will not be done. If study treatment is terminated early by Investigator decision due to patient improvement, the study assessment schedule should be followed as normal.

\+ Study specific procedures must be performed after informed consent for the study is obtained. If ICU standard procedures are in line with the study procedures and if the timing of RAAA diagnosis, consent, operative treatment and dosing preclude repetition of procedures for the purposes of the study, then standard patient care test results may be used for screening even prior to obtaining consent

++ Evaluation of the value before surgery

∇ Study medication, FP-1201-lyo or placebo, is administered as a bolus intravenous injection, followed by a 5 ml flush of sterile saline. On D0, the first dose of study

medication is administered at 0h. Subsequent doses from D1 to D5 are administered every 24 hours ± 1 hour.

❖ SOFA scores are assessed daily in the ICU from D0 post-dose to D30, as applicable by standard clinical treatment at that point. (Therefore, if a patient does not have an arterial line, no arterial blood sampling should be taken.)

** Only for females under age of 60 years.

Table 6: Flow Chart for the Short Term and Mid Term Follow-up Periods

ASSESSMENTS	Short Term Follow-Up*				
	D6	D9**	D13**	D30	D90 (+14 days) 3 months
Check whether patient is in the ICU	X	X	X	X	
Check whether patient is on ventilation	X	X	X	X	
Check whether patient is on organ support (hemodialysis)	X	X	X	X	X
SOFA Scoring ❖ (worst daily value should be used)	X	X	X	X	
Ventilator Free Days (VFDs)				X	
Physical Examination	X	X	X	X	
Vital Signs; Temp, BP, HR (closest to 8am)	X	X	X	X	
Blood Biochemistry	X	X	X	X	
Haematology	X	X	X	X	
Intra-abdominal pressure (IAP) (closest to 8am)	X	X	X		
MxA, CD73 and PIM	X 22h±2h s nce Dose 6	X	X		
NAbs				X D30±5D	
Mortality (reason/diagnosis of death)				X	X
Concomitant Medications/Therapies	←----------X----------→				
AE Recording	←----------X----------→				
Deaths Recording	X				X
mRS					X

KEY:

* Assessments prior to D30 are only performed if patient is still hospitalised in the same hospital initially operated. If the patient is moved to a different hospital, assessments will not be done. If study treatment is terminated early by Investigator decision due to patient improvement, the study assessment schedule should be followed as normal.

** From D6 to D30 assessment of vital signs, patient status and physical examination are performed as scheduled if hospitalised (i.e. in hospital where initially operated). Biochemistry, haematology, MxA, CD73 and PIM are assessed on D9 and D13 if patient is hospitalized. D9 to D30 assessments should be performed at the same time of day as D6 assessments. Note: Where a patient's condition precludes an assessment taking place as scheduled, the assessment should be performed within ± 2 hours of the scheduled time and if this is not possible, the assessment will not be performed and the reason for non-performance will be recorded.

❖ SOFA scores are assessed daily in the ICU from D0 post-dose to D30, as applicable by standard clinical treatment at that point. (Therefore, if a patient does not have an arterial line, no arterial blood sampling should be taken.)

7.2 Assessment of Discontinued Patients

If a patient is discharged from the hospital (to another hospital, home, etc.) **prior to D30**, a complete final evaluation should be made at the day of discharge as described below in table 7.

If a patient is discharged from the hospital (to another hospital, home, etc.) **after D30**, the assessments will be performed in **all** the long-term follow-up time points as described below in table 7.

Table 7: Flow Chart for Discharge Prior to D30 and After D30

ASSESSMENTS	Discharge	
	Prior to D30	After D30
Check whether the patient is in the ICU ❖	X	X
Check whether the patient is on ventilation *	X	X
Check whether the patient is on organ support (hemodialysis)	X	X
SOFAs (the worst daily value should be used)	X	
Ventilator Free Days (VFDs)	X	
Physical Examination	X	
Vital Signs (Temp, BP, HR)	X	
Blood Biochemistry	X	
Haematology	X	
MxA, CD73 and PIM +	X	
Intra-abdominal pressure (IAP) ++	X	
Days on Vasoactive Drugs	X	
Mortality (state the reason of death if possible)**	X	X
Concomitant Medications/Therapies	X	
AE recording	X	
Death recording	X	X

KEY:

❖ Patients still on ICU who are transferred to another hospital or healthcare ICU facility prior to D30 are followed up to assess the days on ICU at scheduled D30 if applicable.

* Patients still on positive pressure ventilation who are transferred to another hospital or healthcare facility prior to D30 are followed up to assess the VFD outcome at scheduled D30.

** Mortality follow-up: For all patients, mortality is assessed at D90 (3 months). If a patient is lost to follow-up, when possible, mortality data will be sought from alternate sources such as the patient's local Physician or available national databases.

\+ Only in case discharge is on D1, D2, D3, D4, D5, D6, D9 or D13.

++ Only in case patient is still on ICU.

7.3 Sequential Organ Failure Assessment (SOFA)

SOFA scores are assessed daily from D0 post-dose to D30 whilst the patient is in the ICU and all daily elements of the SOFA score are available. **Note:** The worst daily value of each element should be used to calculate the overall SOFA score.

Table 8: Schedules for SOFAs

ASSESSMENTS	Baseline Period
	D0 pre-dose
SOFA	

ASSESSMENTS	Treatment Period					
	D0 post dose	D1	D2	D3	D4	D5
SOFA	X	X	X	X	X	X

ASSESSMENTS	Short Term Follow-Up																								
	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22	D23	D24	D25	D26	D27	D28.	D29	D30
SOFA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 9: Modified Ranking Scale (mRS)

The scale runs from 0-6, from perfect health without symptoms to death	
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities
3	Moderate disability. Requires some help, but able to walk unassisted
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent
6	Dead

7.4 Procedures by Visit

7.4.1 *Pre-screening Evaluation and screening log*

Patients will be considered for entry into the study when a diagnosis of RAAA has been made. Before entering the study, patients are assessed to ensure that all eligibility criteria are met. Patients not meeting the eligibility criteria must not be entered into the study.

When considering patients for the study the investigational site will review the following:

- All eligibility criteria are met (refer to Sections 4.1 4.3)
    - In some cases, the amount of time expendable from ER to OR (e.g. severely unstable haemodynamics) may be so limited that an adequate time or state for enrolment cannot be achieved. For these patients a consent from the next of kin can be sought after successful surgery.
    - However, for the possible enrolment of patients, investigational sites must be active in incorporating the pre-study evaluation in their own surgical emergency protocols.

Provision of informed consent. Study specific procedures must be performed after informed consent for the study is given. **Note:** When the ER, OR and ICU standard procedures are in line with study procedures and if the timing of RAAA diagnosis, consent, open aortic repair and dosing preclude repetition of procedures for the purposes of the study, standard patient care test results may be used for screening even prior to consent.

Investigational sites will review all ER patients with symptoms of RAAA in order to identify potential patients for this study. Investigational sites will maintain a log of all RAAA patients seen in their ER and will record the following information:

- Date of admission to ER
- Met and unmet inclusion criteria
- Met and unmet exclusion criteria
- Reason for non-eligibility

If the patient does not enter the study the reason for this will be recorded.

The log is sent to the Sponsor on a monthly basis whilst the investigational site is open for recruitment.

7.4.2 Screening Assessments and Pre-dose Procedures

7.4.2.1 Screening assessments to be performed after diagnosis of RAAA prior to surgical treatment and the first dose of study medication

Screening assessments will be carried out after informed consent is obtained and must be completed before the first dose of study medication is administered. **The first dose of the study medication is administered at arrival to the ICU (latest 4 hours after RAAA operation).**

The following parameters are reviewed and the data is recorded in the eCRF once the patient has been consented (refer to table 5 and the flow chart in figure 1):

- Date and time of informed consent
- Allocated patient screening number
- Medical history including:
  - chronic conditions
  - currently treated conditions
  - concomitant medications
- Review of the inclusion and exclusion criteria
- Demographic data including sex, age at entry and race
- Physical Examination of major body systems including predicted body weight (refer to Section 6.3.4 for the calculation formula) and height
- Recording of concomitant medications and therapies

The data must be collected during the screening assessment but can be entered in the eCRF after surgery.

7.4.2.2 Pre-dose procedures to be performed on D0 before the first dose of study medication is administered

On D0 all pre-dose procedures and assessments are to be performed **before the first dose of study medication**. **Note:** Where a patient's condition precludes an assessment taking place as scheduled, the assessment should be performed as soon as possible. If this is not possible, the assessment will not be performed and the reason for non-performance will be recorded. However, all D0 pre-dose assessments must be performed prior to the first dose of study medication being administered and every effort must be made to perform all assessments.

The following procedures and assessments are performed and the data is recorded in the eCRF (refer to the flow charts in Table 5):

- Review of the inclusion and exclusion criteria to ensure continued eligibility
- Randomisation: randomisation number and date and time of randomisation are recorded
- Hemodynamic collapse before cross clamping (yes/no)
- Vital signs (body temperature, blood pressure, pulse)
- Modified ranking scale (mRS) (evaluation of the value before surgery)
- Blood biochemistry (refer to Section 6.3.2 for specific biochemistry variables)
- Blood pregnancy test if relevant (only for females under age of 60 years)
- Haematology (refer to Section 6.3.2 for specific haematology variables)
- Pharmacodynamics (PD): MxA sample for central testing within 1 hr pre-dose
- Secondary efficacy: Neutralizing antibodies IFN-beta (NAbs) sample within 1 hr pre-dose
- Tentative Disease Specific Marker CD73 and Potential Inflammatory Marker (PIM) samples for central testing within 1 hr pre-dose

- Recording of concomitant medications and therapies
- Collection of Adverse Events from this time point onward: All Adverse Events and Serious Adverse Events will be collected from the time of informed consent signature and throughout the study until the last follow-up visit.
- Recording of major surgical outcomes affecting patient
    - open abdomen (yes/no)
    - left renal vein ligated (yes/no)
    - Clamping time above the renal arteries

In practice, at arrival at the ICU standard artery-astrup analysis for haematology and biochemistry are performed. Tubes for disease and medication specific markers are drawn at the same time and stored in the ICU. After sampling, the study medication is begun. The study medication is also stored in the ICU.

7.5 TREATMENT PERIOD (D0 to D5) and SHORT TERM follow-up period (D6 to D30): STUDY MEDICATION ADMINISTRATION, PATIENT CARE, AND ASSESSMENTS

The study treatment period comprises D0 to D5 inclusive. Most procedures and assessments to be performed on D0 are pre-dose (with the exception of recording of SOFA scoring, concomitant medications and therapies and AE reporting) and they are detailed in Section 7.4.2.2.
The procedures and assessments to be performed on D0 from the time of study medication administration to D5 are detailed in Section 7.5.1.
The procedures and assessments to be performed in the short-term follow-up period are detailed in Section 7.5.2.
Assessments from D0 and prior to D30 are only performed if the patient is hospitalised in the operating hospital (where the patient was operated and recruited in the trial).

7.5.1 Schedule of assessments for D0 to D5

Day 0 0 hrs and post dose:
The first dose of study medication will be administered on D0 at 0 hrs (with maximum of 4 hours after the RAAA surgery). The following D0 study medication administration procedures and post dose assessments are performed (refer to Table 5) and the data is recorded in the eCRF:

- Administration of study medication: FP-1201-lyo or placebo, administered as a bolus intravenous injection, followed by a 5 ml flush of sterile saline
- SOFA score assessment for baseline
- Recording of concomitant medications and therapies
- AE reporting commences after the consent has been obtained.

Day 1 to Day 5:
From D1 to D5 inclusive, the following study assessments and procedures will be performed (patient will not be subjected for additional invasive assessments if not standard for patient care in ICU/hospital ward):

- Check if patient is on ventilation (refer to VFD definition in Section 6.2.3)
- Check if patient is in the ICU

- Check if patient is on organ support
- The number of organ failure free days by means of SOFA. SOFA scores are assessed daily in the ICU (refer to Table 1 and Table 8 for the SOFA composition and schedules. **Note:** The worst daily value of each element should be used to calculate the overall SOFA score.
- Vital signs (temperature, BP and HR) must be measured and recorded between 6 am to 10 am using the values closest to 8 am (assuming these values are representative of the patient's condition). All vital signs assessments must be made at the same time point when possible.
- Blood biochemistry**:** samples must be taken between 6 am to 10 am (refer to Section 6.3.2. for specific biochemistry variables)
- Haematology: samples must be taken between 6 am to 10 am (refer to Section 6.3.2. for specific haematology variables)
- Intra-abdominal pressure (IAP) must be measured daily between 6 am to 10 am during ICU stay or until complete resolution of elevated pressure. Not applicable if abdomen was left open at index operation
- Daily recording of major surgical outcomes affecting patient
  - open abdomen: yes/no (to detect time of closure or re-opening)
  - lower limb embolization (yes/no), consequent rhabdomyolysis (yes/no)
  - Explorative laparotomy for bleeding (yes/no), record blood loss
  - Explorative laparotomy and bowel resection (yes/no)
- MxA, CD73 and PIM samples for central testing within the timeframe of 22 hours ± 2 hours after the previous day's administration of study medication, however before the next study drug dose
- Recording of concomitant medications and therapies
- AE reporting

Note: Where a patient's condition precludes an assessment taking place as scheduled, the assessment should be performed within ±2 hours of the scheduled time and, if this is not possible, the assessment will not be performed and the reason for non-performance will be recorded. However, every effort must be made to perform all assessments.

Each day on D0 to D5 inclusive, the study medication, FP-1201-lyo or placebo, is administered as a bolus intravenous injection **24 hours ± 1 hour after the previous day's administration of study medication** and the following study assessments and procedures are performed **post study medication administration:**

- Recording of concomitant medications and therapies
- AE reporting commences after obtaining the informed consent.

7.5.2 Schedule of assessments for the short-term follow-up period (D6 to D30)

Daily assessments are performed up to D30 if the study patient is still hospitalized in the same hospital where initially operated. If the patient is moved to a different hospital (or home), assessments will not be done. All assessments should be performed at the same time of a day as the D6 assessments were performed. **Note:**

Where the patient's condition precludes an assessment taking place as scheduled, the assessment should be performed within ± 2 hours of the scheduled time, and if this is not possible, then the assessment will not be performed and the reason for non-performance will be recorded. However, every effort must be made to perform all assessments.
The following study assessments and procedures will be performed as below from D6 to D30 (refer to flow charts in Table 6):

- Check if patient is on ventilation (refer to VFD definition in Section 6.2.3)
  Patients still on positive pressure ventilation who are transferred to another hospital or healthcare facility prior to D30 will be followed up to assess the VFD outcome at D30.
- Check if patient is in the ICU
  Patients still on ICU who are transferred to another hospital or healthcare ICU facility prior to D30 will be followed up to assess the days on ICU at D30.
- Check if patient is on organ support
- The number of organ failure free days by means of SOFA (arterial blood gas analysis should not be done if not part of standard care at this point).
- Physical Examination of major body systems
- Vital signs (temperature, BP and HR) must be measured and recorded between 6 am to 10 am using the values closest to 8 am (assuming these are representative of the patient's condition). All vital signs assessments must be made at the same time point when possible.
- Blood biochemistry **D6 and D30 only**, and D9 and D13 if patient is hospitalised. Samples must be taken between 6 am to 10 am (refer to Section 6.3.2. for specific biochemistry variables)
- Haematology **D6 and D30 only**, and D9 and D13 if patient is hospitalised. Samples must be taken at the same time of day as D6 assessments (refer to Section 6.3.2. for specific haematology variables)
- Intra-abdominal pressure (IAP) must be measured daily between 6 am to 10 am during ICU stay or until complete resolution of elevated pressure
- On D6 MxA, CD73 and PIM samples for central testing within the timeframe of 22 hours ± 2 hours after the previous day's administration of study medication. In addition, on D9 and on D13 between 6 am to 10 am, if the patient is hospitalised.
- Neutralizing antibodies IFN-beta (NAbs) sample **D30 only**. For this assessment there is ±5D visit window.
- Days on vasoactive drugs
- Mortality (ICU and hospital) at **D30 only**
- Recording of concomitant medications and therapies
- AE reporting

7.6 Discharge

7.6.1 Discharge prior to D30

If a patient is discharged from the operating hospital prior to D30 and not discontinued, a complete **final evaluation** should be made **at the day of discharge** as described below (refer to Table 7):

- Check if patient is on ventilation (refer to VFD definition in Section 6.2.3)
  All patients, whether still on or already off positive pressure ventilation, who are transferred to another hospital or healthcare facility prior to D30 will be followed up to assess the VFD outcome at D30.
- Check if patient is in the ICU
  Patients that are transferred to another hospital or healthcare ICU facility prior to D30 will be followed up to assess the days in ICU at D30.
- Check if patient is on organ support
- The number of organ failure free days by means of SOFA (arterial blood gas analysis should not be done if not part of standard care at this point).
- Physical Examination of major body systems
- Vital signs (temperature, BP and HR) must be measured and recorded between 6 am to 10 am using the values closest to 8 am (assuming these values are representative of the patient's condition). All vital signs assessments must be made at the same time point when possible.
- Intra-abdominal pressure (IAP) must be measured daily between 6 am to 10 am during ICU stay or complete resolution of elevated pressure
- Days on vasoactive drugs
- Recording of concomitant medications and therapies
- AE reporting
- Patient is invited for a laboratory visit to assess NAbs and other D30 assessments on D30.
- Mortality follow-up: For all patients who withdraw from the study prior to D30, mortality will be assessed at D30 and D90 (3 months). **Note:** A time window of +14 days is given for D90 assessment.

In the case of an ongoing AE, appropriate safety evaluations and/or additional tests may be performed at any time when clinically indicated at the discretion of the Investigator, until resolution or D30, whichever is the sooner.

Any ongoing AEs should be followed up to resolution or study D30, whichever is the sooner.

If the patient refuses any of the above assessments or is lost to follow-up, this is noted in the eCRF.

If a patient is lost to follow-up, mortality data will be sought from alternate sources such as the patient's local physician or available national databases, whenever possible.

7.7 Final FOLLOW-UP at D90 (3 months)

The study has a final follow up at D90 (3 months) for assessment of the final outcome, need of organ support (mainly hemodialysis), and use of health care services. Modified ranking scale (mRS) at D90 will be used to evaluate study subject disability. Data will be gathered from patient charts, national databases or by phone directly from the patient or a health care facility. If a patient is on hemodialysis at D90, it is considered as permanent in this study. Acute renal failure related to RAAA often resolves within 3 months if it is reversible.

If the patient refuses any of the above assessments or is lost to follow-up, this is noted in the eCRF.

8 STATISTICAL METHODS

Detailed information regarding statistical methods will be provided separately in the Statistical Analysis Plan (SAP). Any deviations from the planned analyses specified within the SAP will be justified in writing and presented within the final clinical study report.

8.1 Populations for analysis

The following analysis sets will be defined for statistical analysis:

The Full Analysis Set for Efficacy (FAS-E) consists of all randomised patients receiving study treatment but excluding the early deaths (within 36 hours from first dose of the study treatment) and comprises the analysis set on which the primary efficacy analysis is based.

The Per Protocol Set (PPS) consists of the patients in the FAS excluding patients with major protocol violations. A relevant list of the major protocol violations will be detailed in the SAP. The precise definition of the PPS at the patient level will be identified at the blind review conducted both before interim and final analysis.

Statistical analyses for the primary and secondary endpoints are performed on both the FAS-E and PPS.

The Full Analysis Set for Safety (FAS-S) consists of all randomised patients receiving study treatment and comprises the analysis set on which the evaluation of safety is based. A patient receiving the wrong treatment according to the randomisation will be analysed for safety and tolerability in the treatment group corresponding to the treatment received.

8.2 Sample size estimation

The primary efficacy endpoint is all cause mortality at D30. Death within 36 hours from the first dose of the study treatment leads to exclusion from efficacy analysis (see section 8.5.1 Efficacy Analysis).

A sample size of 129 eligible patients for the primary efficacy analysis, with a 2:1 ratio to active (86) and placebo (43), will detect the difference of 22% between the two treatment groups with 80 % power using 2-sided test with 0,05 significance level. Because of the planned interim analyses, the calculations assume that 2 sequential tests are made and the O'Brien-Fleming spending function is used to determine the test boundaries.

Power calculation assumes 37 % proportion of events on placebo group and 15 % proportion for the active treatment group.

To achieve a sample size of 129 for the primary efficacy analysis, taking account the estimated amount of early deaths within 36 hours from first dose of the study treatment (estimated 15 %), there should be 152 patients randomised to the study.

The sample size calculations will be re-evaluated after the interim has been performed (comprising at least 31 eligible patients for the primary efficacy analysis).

8.3 BASELINE CHARACTERISTICS AND DISPOSITION

As per Section 6.4., the baseline assessments consist of those assessments carried out in the screening period and those carried out prior to the first dose of the study medication on D0.

Demographic and baseline characteristics are summarised by treatment group and overall.

Disposition and reasons for discontinuation are summarised for all patients together with treatment exposure and study duration by treatment group.

8.4 Evaluation of safety

All patients who receive a minimum of one administration of study medication are included in the safety analysis.

Adverse Events

Treatment Emergent Adverse Effects (TEAEs) and SAEs are classified according to the Medical Dictionary for Regulatory Activities (MedDRA) SOC and the preferred term. The incidence of these events will be summarised by treatment group in tables which will also include information on severity and relationship to study medication. These summaries will be based on the Safety Set. The frequency of complications is summarised by treatment groups in terms of counts.

Vital Signs

Vital signs data (BP, HR and temperature) is summarised by treatment group separately at D0, D1, D2, D3, D4, D5, D6, D9, D13 and D30. The maximum change from baseline over the 30-day follow-up period will be calculated for each patient and summarised.

Vital signs summaries will be in terms of mean, median, standard deviation (SD), minimum and maximum.

Clinical Laboratory Parameters

Descriptive statistics (mean, median, SD, minimum and maximum) for biochemistry and haematology will be obtained and tabulated by treatment group at D0, D1, D2, D3, D4, D5, D6 and D30. Descriptive statistics (mean, median, SD, minimum and maximum).

Shift tables (within, below and above the normal range) will also be provided for each parameter in relation to the maximum change from baseline from D0 over the complete 30-day follow-up period.

8.5 Evaluation of efficacy

8.5.1 *Evaluation of primary efficacy endpoint*

The primary endpoint of the study will be:

- All-cause mortality at D30

To be eligible for efficacy analysis each patient must receive at least two doses of the study medication with an effect time of 12 hours after second dose. This means that a death within 36 hours from the first dose of study treatment leads to exclusion from efficacy analysis. This derives from the fact that based on the prior clinical phase I/II studies with interferon beta-1a, its effect on the expression of CD73 and production of adenosine will require 12 to 24 hours from administration of the drug. Thus, therapeutic levels will not be reached until 12 hours from the second dose, i.e. 36 hours from the first dose. Measuring efficacy against multi-organ failure prior to this point is misleading because therapeutic levels have not yet been reached.

The efficacy analyses will be conducted using logistic regression model for the observed mortality rates in the two treatment groups. Stratification factors used in the randomisation will be included in the model. Primary result will be presented as an adjusted odds ratio and a 95% CI for the adjusted odds ratio. Also, a 95% confidence interval (CI) for the difference in the observed mortality rates will be calculated. A two-sided significance level of 0.05 will be used for all analyses.

There will additionally be an evaluation of the homogeneity of the treatment effect by investigating treatment by centre and treatment by baseline factor interactions in the logistic model. Data for the primary efficacy endpoint will also be presented for key, pre-defined subgroups of patients together with 95% CIs for the difference in those rates to supplement the investigation of homogeneity. Mortality at D30 will be illustrated also using survival function and Kaplan-Meier curves including log-rank test as an exploratory analysis.

8.5.2 *Evaluation of secondary efficacy endpoints*

By way of further confirmatory measures of efficacy, the following endpoints will be analysed:

- Time and reason/diagnosis of death up to D90 (3 months)
- Number of VFDs up to D30
- Number of days receiving hemodialysis at D30 and D90
- Number of ICU free days up to D30
- Organ failure free days up to D30
- Neutralizing antibodies IFN beta (NAbs) in whole blood samples up to D30
- Number of days in hospital up to D30 and D90 (length of stay in another health care facility)
- Prevalence of abdominal compartment syndrome, i.e. intra-abdominal pressure (IAP) value differences between study groups
- Disability on D90 measured by modified ranking scale (mRS)

All-cause mortality at D90 (3 months) will be compared using methods for the evaluation of time to event endpoints. Hazard ratios for each of these time periods will be presented with associated 95% CIs and log-rank p-values for the FAS. Also, similar logistic regression model than for the primary endpoint (D30 mortality) will be done.

For endpoints number of VFDs, number of ICU free days, organ failure-free days, number of days on hemodialysis, IAP values data will be summarised in terms of the mean, median, minimum and maximum, and the treatment groups will be compared using the Mann-Whitney U-test. Complete data on organ failure free days may be unavailable due to SOFA scores not being assessed after ICU treatment. To account for this, the number of organ failure free days will be analysed by expressing these as a proportion of the days on which SOFA scores are available. Disability measured with mRS will be summarized descriptively and the treatment groups will be compared using the Cochran-Mantel-Haenzel test.

All secondary analyses are designed to be supportive of the analysis of the primary endpoint and there will be no adjustments for the multiplicity of endpoints so that each analysis will be undertaken at the two-sided 5% level of significance.

8.6 INTERIM ANALYSIS

An interim analysis will be performed after there are 1) at least 31 and 2) 84 patients that are eligible for the primary efficacy endpoint analysis (excluding early deaths within 36 hours from first dose of study treatment, similarly than for primary analysis). At this point the study can be stopped for efficacy or futility depending on the interim analysis results. The first interim is brought further up as the recruitment rate has markedly stagnated, mainly due to changes in treatment practices of RAAA. The sample size calculations will be re-evaluated after the first interim.

Primary efficacy endpoint will be evaluated using O'Brien and Fleming criteria controlling the type I error rate. If the study goal is reached, the study can be stopped early for efficacy. The first interim analysis focuses mainly for the futility stopping, as the power is low to reach the efficacy criteria. The power to reach the study goal at the second interim analysis with 84 evaluable patients is approximately 40%, but also this calculation will be re-evaluated after the first interim.

In addition, there will possibility to stop the study for futility at the interim analyses. Predefined criteria for futility stopping will be defined in the interim analysis plan.

Statistical analysis plan for the final and interim analysis will be prepared before the interim analysis. A blind review of data will be performed before the interim analysis to confirm analysis assumptions for e.g. overall number of events.

9 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

9.1 Data Quality Assurance

The Sponsor or Sponsor's designee will conduct a site visit to each study centre to verify the qualifications of each Investigator, inspect the site facilities and inform the Investigator of their responsibilities and the procedures for ensuring adequate and correct documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded in the eCRF for this study must be consistent with the patients' source documentation (i.e., medical records).

9.1.1 *Database Management and Quality Control*

All study-related data generated by site personnel will be captured electronically at each study centre using the eCRF.

Central laboratory assays (e.g., PD) will be managed by the central laboratories and results will be transferred for inclusion in the study analysis database.

Once the eCRF clinical data have been submitted, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, and the time and date will be logged to provide an audit trail.

The specific procedures to be used for data entry and query resolution using the eCRF will be provided to study sites in eCRF completion instructions. In addition, site personnel will receive training on the eCRF. Once the source data verification is complete and all queries are closed, Data Management will freeze the eCRF page.

9.2 Case Report Forms and Source Documentation

All data obtained during this study must be promptly entered in the eCRF. All source documents from which eCRF entries are derived should be placed in the patient's medical records. Measurements for which source documents are usually available include laboratory assessments.

Data that will be entered directly into the eCRF (i.e., for which there is no prior written or electronic record) are considered source data.

The eCRF entries for each patient will be checked against source documents at the study site by the CRA.

9.2.1 *Data Collection*

The Investigators (and appropriately authorised staff) will be given access to an online web-based electronic data-capture system that is compliant with US Food and Drug Administration Title 21 Code of Federal Regulations Part 11. This system is specifically designed for the collection of clinical data in electronic format. Access rights to the electronic data-capture system will be carefully controlled and configured according to each individual's role throughout the study. Only the Investigator and authorised staff will be able to enter and correct data in the eCRF.

The eCRF should be completed for each patient included in the study and should reflect the latest observations on the patients participating in the study. Therefore, the eCRF is to be completed as soon as possible during or immediately after the patient's visit or assessment. The Investigator must verify that all data entries in the eCRF are

accurate and correct. If some assessments cannot be done, or if certain information is unavailable, not applicable or unknown, the Investigator should indicate this in the eCRF.

Computerised data-check programs and manual checks will identify any data discrepancies for resolution. Corresponding queries will be generated in the system and the site will be informed online about new issues to be resolved. All discrepancies must be resolved online directly by the Investigator or by staff authorised to do this by Delegation of Authority.

After completion, the Investigator will be required to electronically sign off the clinical data.

9.3 **Access to Source Data**

During the study, the CRO site CRA will make regular site visits to review protocol compliance, conduct source data verification by comparing eCRF entries and individual patient's medical records, assess drug accountability and management, assess laboratory procedures and ensure that the study is being conducted according to pertinent regulatory and protocol requirements. The review of medical records will be performed in a manner that ensures patient confidentiality is maintained.

Source data verification will be required to monitor the progress of the study. Moreover, regulatory authority, IECs and/or the Sponsor's Clinical Quality Assurance Group or designee may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator must assure the CRO and the Sponsor that they will provide the necessary support at all times.

9.4 **Archiving Study Records**

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable legal requirements. For example, in Finland data needs to be stored at least for 15 years.

9.5 **Good Clinical Practice**

The procedures set out in this study protocol are designed to ensure that the Sponsor and Investigator abide by the principles of the Good Clinical Practice guidelines of the ICH and the Declaration of Helsinki.(Declaration of Helsinki 2013) The study will also be carried out in keeping with local legal requirements.

9.6 **Informed Consent**

The Investigator at each investigational site is responsible for ensuring that informed consent (written signed or witnessed) for study participation is given by each patient prior to collection of study data and administration of the study drug. The informed consent should be sought from the patient, but due to emergency nature of the condition it may be in the best interest of the patient to move straight on for surgery

and an adequate amount of time cannot be spent on consenting. This will be determined by the investigator in the best interest of the patient. In such a case the investigator can seek informed consent from the next of kin during a four-hour time period when the patient moves from the OR to the ICU and the drug must be administered.

If consent has not been obtained, a patient cannot be randomised into the study.

If a protocol amendment is required, the ICD may need to be revised to reflect those changes. If the ICD is revised, it must be reviewed and approved by the appropriate IEC, and signed by all patients (or their representatives) subsequently enrolled in the study as well as those currently enrolled in the study.

9.6.1. Consent Procedure

Informed consent must be obtained from the patient. The patient is informed about the study by the Principal Investigator or by a member of the research team to whom the Principal Investigator has allowed delegation of the consent process.

The patient is given a copy of the Patient Informed Consent Document (PICD). Informed patients are given an adequate amount of time to consider their decision about entering the study. However, the requirement to initiate surgery can significantly limit the amount of time available and the operating vascular surgeon will determine the time that may be used for this, as considered best for the patient.

If a patient decides to enter the study he or she is asked to sign the consent. If the patient is unable to sign the consent document due to ongoing preparations for operation or e.g. stomach pain, or any other relevant reason, and inability to sit up for signing, a verbal consent can be given with a witness of one members of medical staff excluding the study personnel. The consent document is then countersigned by a member of the study team to whom obtaining of consent has been delegated. One copy of the document is retained by the patient. Another copy is placed in the patient's medical records (only if it is required locally). The original document is retained in the Investigator Site File.

If there is not adequate time to consent the patient prior to surgery, but otherwise the patient would be eligible for the study (complete unconsciousness leads to exclusion), the investigator can seek consent from the next of kin after the surgery. If this approach is taken written informed consent needs to be taken from the study subject at the soonest possible moment.

9.6.2. Withdrawal of Consent

Patients may withdraw from the study at any time, for any reason and such a decision will not affect standard care given to the patient. Data recorded up to the point of withdrawal is included in the study analysis.

If a patient requests termination of the administration of study medication during the treatment period, the administration of study medication is terminated but the patient will continue in the study and all follow-up assessments are performed.

If a patient withdraws consent during the treatment period, the administration of study medication is terminated and no further active study assessments are performed from that point on. However, permission will be sought to access the patient's medical records for data relevant to the study (e.g., mortality, Ventilator Free Days [VFDs] etc.) and the patient will be asked to complete the D30 physical follow up.

If a patient withdraws consent after the treatment period then no further active study assessments will be performed from that point on. However, permission will be sought to access the patient's medical records for data relevant to the study (e.g., mortality, VFDs, etc.) and the patient will be asked to complete the D30 physical follow up.

9.7. Protocol Approval and Amendment

For the study to start, all required documentation must be approved by the IEC and Competent Authority, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IEC/competent authority approval prior to an implementation (if appropriate).

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

9.8. Independent Data Monitoring Committee

An IDMC will be established for the study. The duty of the committee is to protect ethical and safety interests of patients and all others who may possibly be exposed to the study medication and to make recommendations to the investigators. The IDMC will review safety data retrieved for interim analysis (i.e. AEs and SAEs) in an unblinded manner and will give recommendations to the Sponsor regarding study modification and/or termination. The IDMC will comprise at least three members, including at least one independent biostatistician and two clinicians not otherwise involved in the study.

An IDMC charter is established, which documents in more detail the responsibilities, duties and objectives of the individuals and of the committee.

9.9. Premature Termination of the Study

The Sponsor reserves the right to stop the study at any time on the basis of new information regarding safety or efficacy (e.g., discovery of an unexpected, significant or unacceptable risk to the patients enrolled in the study), or if study progress is unsatisfactory (e.g., failure to enrol patients at an acceptable rate), or for other valid reasons (e.g., Sponsor decides to suspend or discontinue development of the drug). After such a decision is made, the Investigator must inform all on-study patients within 1 week. All delivered study materials must be collected and all eCRF pages completed to the extent possible.

9.10. Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and members of their research team must not disclose any information without prior written approval from the Sponsor.

The anonymity of participating patients must be maintained. Only patient number (code) will be recorded in the eCRF. Documents that identify the patient will be coded by using only patient number codes.

9.11. Other Ethical and Regulatory Issues

If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the Sponsor will issue prompt notification to all parties regulatory authorities, Investigators and IEC/ EC.

A significant safety issue is one that has a significant impact on the course of the clinical study or programme (including the potential for suspension of the development programme or amendments to protocols) or warrants immediate update of informed consent.

9.12. Publication Policy

Any manuscript, abstract or other publication or presentation of results or information arising in connection with the study (including any ancillary study involving study patients) must be prepared in conjunction with the study Sponsor and must be submitted to the Sponsor for review and comment at least 45 days prior to submission for publication or presentation. No single centre or groups of centres may publish individually. The Sponsor's comments on the proposed publication shall be considered in good faith by the authors. The Sponsor may delay such submission by a maximum of 90 days if it reasonably believes that publication of results may compromise its intellectual property rights or may insist that such information or data is removed from the proposed publication. Publication of the results will not include confidential information without the permission of the Sponsor.

The original eCRF pages and all data generated during the study under this protocol will become the property of the Sponsor.

The Sponsor may announce quality-assured summary data in order to comply with the requirements of financial regulatory authorities, while ensuring so far as possible that such announcements will not compromise the Investigators' ability to publish the data in appropriate scientific forums.

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