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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Study code: INFORAAA

Phase II study

STATISTICAL ANALYSIS PLAN

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Date

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Date

[redacted]

[redacted] Responsible person from the Sponsor

[redacted]

Date

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1 Abbreviations

AE	Adverse event
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical
FAS-E	Full analysis set for efficacy
FAS-S	Full analysis set for safety
IAP	Intra-abdominal pressure
ICU	Intensive care unit
MedDRA	Medical dictionary of regulatory authorities
mRS	Modified ranking scale
NAb	Neutralizing antibody
PD	Pharmacodynamics
PIM	Potential Inflammatory Markers
PPS	Per protocol set
SD	Standard deviation
SAE	Serious adverse event
SOFA	Sequential organ failure assessment
TEAE	Treatment emergent adverse event
VFD	Ventilator free day

2 General remark

This SAP version further details the SAP dated 17.6.2019, which was generated before performing the Interim analysis for the 35 evaluable patients. Study was discontinued after the Interim analysis. The earlier version of the SAP concentrated on the primary analyses and this version will entail all planned analyses. The analysis plans concerning the primary analyses are not changed from the previous version.

As the study was discontinued, analyses described here, will be performed on the available data gathered thus far.

3 Study objective(s)

The primary objective of this study is to evaluate the safety and the efficacy of FP-1201-lyo over placebo on all-cause mortality at study day 30; D30 (30 days from the first dose of study medication).

The secondary objectives of this study are

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) IL-6 and HGF
5. To evaluate neutralizing antibodies against IFN beta-1a (NAbs)

4 Design and type of the study

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.

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.

With an estimated screening failure rate of approximately 15%, a maximum of 180 patients were planned to be consented and entered into the study in order to randomise and initiate treatment of 152 patients.

Study was discontinued after an Interim analysis.

5 Study variables

The following variables will be evaluated

<u>The demographic and baseline variables</u>

Gender, age at entry, race, weight (predicted or actual), height, medical history, concomitant medications/therapies, major surgical outcomes affecting patient and pregnancy test (females of child bearing potential, and peri procedural information (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 and recycling of blood during surgery (yes/no)).

<u>The primary efficacy outcome variable</u>

- All-cause mortality at D30

<u>The secondary efficacy outcome variables</u>

- 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 treatment groups
- Neutralizing antibodies against IFN beta (NAbs) in whole blood samples up to D30

- Disability on D90 measured by modified ranking scale (mRS)

Safety variables

Adverse events, vital signs (body temperature, blood pressure, heart rate), physical examination and clinical laboratory parameters (biochemistry and haematology).

Pharmacodynamic (PD) and tentative disease specific marker variables

- MxA (protein) concentration in whole blood samples from baseline up to D13
- CD73 concentration in serum samples from baseline up to D6
- Potential Inflammatory Markers (IL-6 and HGF) in serum samples from baseline up to D13

Pharmacoeconomic variables

- 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

6 Sample size considerations

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. 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 z-test with 0.05 significance level. To take account of the planned interim analysis, calculations assume that 2 sequential tests are made (in addition to final analysis) and the O'Brien-Fleming spending function is used to determine the test boundaries. Statistical analysis plan for the interim analyses will be presented in a separate document.

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.

Study was discontinued after the first Interim analysis. Therefore, the sample size did not reach the 129 patients aimed for.

7 Statistical hypotheses

The primary objective of this study is to evaluate the safety and the efficacy of FP-1201-lyo over placebo on reducing all-cause mortality at study day 30, i.e., the null-hypothesis to be tested is

H_0 : FP-1201-lyo is not superior to control with respect to all-cause mortality at study day 30

against

H_1 : FP-1201-lyo is superior to control with respect to all-cause mortality at study day 30

8 Analysis datasets

Statistical analyses will be performed on the following analysis datasets.

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 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-E excluding patients with major protocol violations possibly affecting the primary study endpoint analysis.

The precise definition of the PPS at the patient level was planned to be identified at the blind review conducted both before the second interim and final analysis. The detailed criteria for patient classification will be prepared before database lock. Subject classification was to be created first for the subjects included in the second interim analysis, and later amended for the final analysis with the subjects that were not included in the interim analysis.

The first Interim analysis (after 35 evaluable patients) was based on FAS-E dataset. No classification for PPS was done for the first Interim analysis.

Statistical analyses for efficacy, PD, tentative disease specific markers and pharmacoeconomic variables are performed on both the FAS-E and PPS.

Study was discontinued after the first interim analysis. Subject classification document defining the analysis datasets in detail will be prepared and signed before database lock.

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. All safety analyses are performed on the FAS-S analysis dataset.

9 General statistical considerations

Summary statistics will include at least the number of subjects, mean, standard deviation, median, minimum and maximum for continuous variables, and frequencies and percentages for categorical variables. All data collected will be listed by subject.

In the statistical analyses a p-value less than 0.05 will be considered as an indication of statistical significance. If not stated otherwise, all tests will be performed as two-sided tests and two-sided 95% confidence intervals will be produced. Missing values will not be imputed in the analyses.

9.1 Adjustment for covariates

The primary model will include the stratification factors (age group and gender) used in the randomisation as covariates.

9.2 Handling of drop-outs or missing data

Missing values will not be imputed. Primary endpoint is mortality at Day 30 and all evaluable patients will be included in the primary analysis.

9.3 Interim analyses and data monitoring

Two Interim analyses were planned for the study with futility and efficacy stopping criteria using O'Brien-Fleming boundaries.

Study was discontinued after the first interim analysis.

9.4 Multicenter studies

Handling of centers was to be defined before second interim analysis when there would be better understanding of the center size.

Study was discontinued after the first interim analysis. Patient accrual to the different study centers was varying in amounts. Center info will not be used directly in the analyses, but country and site will be included in the tabulations of patient demographics.

9.5 Multiple comparison/multiplicity

There is one primary efficacy variable in the primary hypothesis of this study; all-cause mortality at D30. The primary evaluation of this hypothesis will be based upon the FAS-E dataset. This in itself will not give reason to adjustments for multiple comparison/multiplicity.

However, two interim analyses were to be performed after reaching 35 and 84 evaluable patients for the primary efficacy variable. For this reason, the primary efficacy endpoint was to be evaluated using O'Brien and Fleming criteria controlling the type I error rate. Using the O'Brien-Fleming spending function on the two sequential tests will cause the nominal alpha level for the primary efficacy variable in final analysis to be 0.04664. Therefore, for the primary efficacy variable a p-value less than 0.04664 will be considered as statistically significant.

As the study was discontinued after the first interim analysis, the planned O'Brien and Fleming correction will not be applied to the primary analysis. Instead, the standard p-value of less than 0.05 will be considered statistically significant.

9.6 Examination of subgroups

Data for the primary efficacy endpoint will also be presented for key, pre-defined subgroups of patients. Concomitant use of glucocorticoids will be one key subgroup as earlier studies have suggested that it may have effect on the study treatment. As CD73 response (and IL-6 and HIF-1α) may be also genetically determined/individual, another key subgroups will be CD73 responder status (determined by a 2-fold elevation in CD 73 (from baseline to peak value). In addition, if analyses indicate yet another, but currently unknown but relevant subgroups, they will be analysed as separate subgroup analyses for exploratory purposes

Key subgroups included in analyses

- Concomitant use of glucocorticoids
- CD 73 responder status (responders vs. non-responders)
- IL-6 responder status
- HIF-1α responder status

10 Demographic and other baseline characteristics

Number of patients enrolled into the study at screening and the reasons for screening failures will be summarized. The number of patients entering and completing the study will be summarized. All patients discontinuing the study will be summarized together with the reason(s) for discontinuation.

Demographic and baseline characteristics will be summarized by treatment using descriptive statistics. Following variables will be analysed.

- Gender
- Age at entry
- Race
- Height
- Weight
    - If actual weight is not available for a patient, then predicted body weight will be used in its place
    - Predicted body weight (kg) is calculated using the following formulae:
        - Males: 50 + 0.91(height in cm – 152.4)
        - Females: 45.5 + 0.91(height in cm – 152.4)
- Major surgical outcomes affecting patient
    - Open abdomen (yes/no)
    - Left renal vein ligated (yes/no)
    - Clamping time above the renal arteries
- Medical history
- Concomitant medications/therapies
- Pregnancy test (females of child bearing potential).

Similarly, the duration of the surgical procedure and peri procedural information will be summarized by treatment. Additional concomitant procedures will be listed only.

Medical history and concomitant medications/therapies will be presented only by frequency and subject count-based tables according to WHO Anatomical Therapeutic Chemical (ATC) classification.

Pregnancy test results (females of child-bearing potential) will be presented only descriptively by a subject count-based table.

11 Extent of exposure and compliance

Treatment exposure, study duration and treatment compliance will be summarised by treatment groups using descriptive statistics.

12 Analysis of efficacy

12.1.1 Primary efficacy variables

Primary efficacy variable is the all-cause mortality at D30. The primary efficacy analysis will be conducted using logistic regression model for the observed mortality rates in the two treatment groups. Stratification factors sex and age 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% exact unconditional confidence interval (CI) for the difference in the observed mortality rates will be calculated. As a sensitivity analysis, unadjusted results will also be presented.

For the primary comparison, a p-value less than 0.04664 was planned to be considered as statistically significant due to O'Brien-Fleming alpha spending used for the Interim analyses. Due to the study discontinuation after the first Interim analysis, two-sided significance level of 0.05 will be used for all analyses.

12.2 Secondary efficacy variables

The following secondary 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*
- Number of ICU free days up to D30*
- Organ failure free days up to D30
- Number of days in hospital up to D30 (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)
- Neutralizing (and anti-drug) antibodies IFN beta (ADAs and NAbs) in whole blood samples up to D30

*ICU free days and number of days in hospital, length of stay in another health care facility and number of days receiving hemodialysis at D90 summarized in pharmacoeconomic tables

All-cause mortality at D90 (3 months) will be compared using Cox regression model including stratification factors (if feasible). Estimated hazard ratios will be presented with associated 95% CIs and log-rank p-values for the FAS-E. Also, similar logistic regression as 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, number of days in hospital, length of stay in another health care facility and 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. Descriptive tables of IAP grade by timepoint will be presented using counts and percentages. Number of days on hemodialysis, number of days in hospital, length of stay in another health care facility and IAP value analyses will be performed for all patients and excluding deaths separately.

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-Haenszel test for trend.

ADAs and NAbs in whole blood samples up to D30 will be summarized using descriptive statistics.

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.

12.3 Additional analyses

Additional analyses are performed on PD and tentative disease specific marker variables and pharmacoeconomic variables.

12.3.1 Pharmacodynamics and tentative disease specific marker analysis

PD and tentative disease specific marker variables to be analysed are MxA concentration in whole blood samples from baseline up to D13, CD73 concentration in serum samples from baseline up to D6 and potential Inflammatory Markers (e.g. IL-6 and HIF-1α) in serum samples from baseline up to D13.

These will be summarised using descriptive statistics and analysed using Repeated measurements ANOVA model with main effects of treatment and day and their interaction. Correlations between the repeated observations will be modelled using compound symmetry covariance structure. The model will be used to estimate population geometric means (95 % CI) for the treatment groups by timepoint.

12.3.2 Pharmacoeconomic analysis

Following pharmacoeconomic endpoints were defined for the study:

- Length of ICU stay, in terms of ICU free days at D90
- 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 (at D90)

Due to early discontinuation of the study, these endpoints will not be analysed.

13 Analysis of safety and tolerability

All subjects in the SAF-S analysis set (all randomised patients receiving study treatment) will be included in the safety and tolerability analysis. Safety variables to be analysed are; adverse events, clinical laboratory parameters, vital signs and physical examination.

13.1 Adverse events

All recorded adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Treatment emergent adverse event (TEAE) is defined as an AE that begins or worsens in severity after at least one dose of study drug has been administered. Non-treatment emergent AEs are listed only.

TEAEs will be summarized using frequency and subject based tables. TEAEs will be tabulated by treatment group, system organ class (SOC), preferred term (PT), causality and severity. For analysis purposes, each subject will also be categorized by the maximum severity reported for a given TEAE and these will be tabulated by maximum severity. TEAEs will be summarized separately for treatment period (D1-D5) and short-term follow-up period (D6-D30). TEAEs are not collected, and therefore not reported, during the mid-term follow-up.

Serious adverse events (SAEs) and AEs leading to discontinuation will be summarized by treatment groups. All deaths up to D90 are reported as SAEs.

13.2 Laboratory safety variables

Laboratory safety variables (biochemistry and haematology) to be analyzed are presented in table 1 below. Descriptive statistics and the frequency and percentage of absolute values below, within and above the reference range will be tabulated for the safety laboratory variables at D0 (baseline), D1, D2, D3, D4, D5, D6, D9, D13 and D30. Descriptive statistics will include mean, median, standard deviation (SD), minimum and maximum.

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

Table 1. Laboratory Variables

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

13.3 Other safety variables

Other safety variable to be analysed are vital signs (body temperature, blood pressure, heart rate) and physical examination.

Vital signs data is summarized by treatment groups separately at D0, D1, D2, D3, D4, D5, D6, D9, D13 and D30. Absolute values and changes from baseline are both summarized. In addition, the maximum change from baseline over the 30-day follow-up period will be calculated for each patient and summarized. Vital signs summaries will be in terms of mean, median, SD, minimum and maximum.

Physical examination covering all the major organ systems will be performed at screening and D30. These will be summarized by treatment groups and visits using frequency and percentage of normal/abnormal observations. In addition, shift tables will be provided describing the change from screening to D30.

14 Completion and premature discontinuation

Completion and premature discontinuation will be listed. The reasons for premature discontinuation will be presented.

15 Deviations from the analyses planned in the study protocol

Study was discontinued after the first Interim analysis. Due to the early discontinuation, the planned O'Brien and Fleming correction will not be applied to the primary analysis. Instead, the standard p-value of less than 0.05 will be considered statistically significant.

Due to low number of accrued patients, the center effect was not further explored in the analyses. Analysis of study centers was limited to summary statistics for baseline information.

Due to the early discontinuation of the study, the pharmacoeconomic endpoints (see section 12.3.2) will not be analysed.

There are no other major deviations in the statistical analysis plan from the analyses planned in the study protocol.

16 Execution of statistical analyses

Statistical analyses will be performed by [redacted].

17 Hardware and software

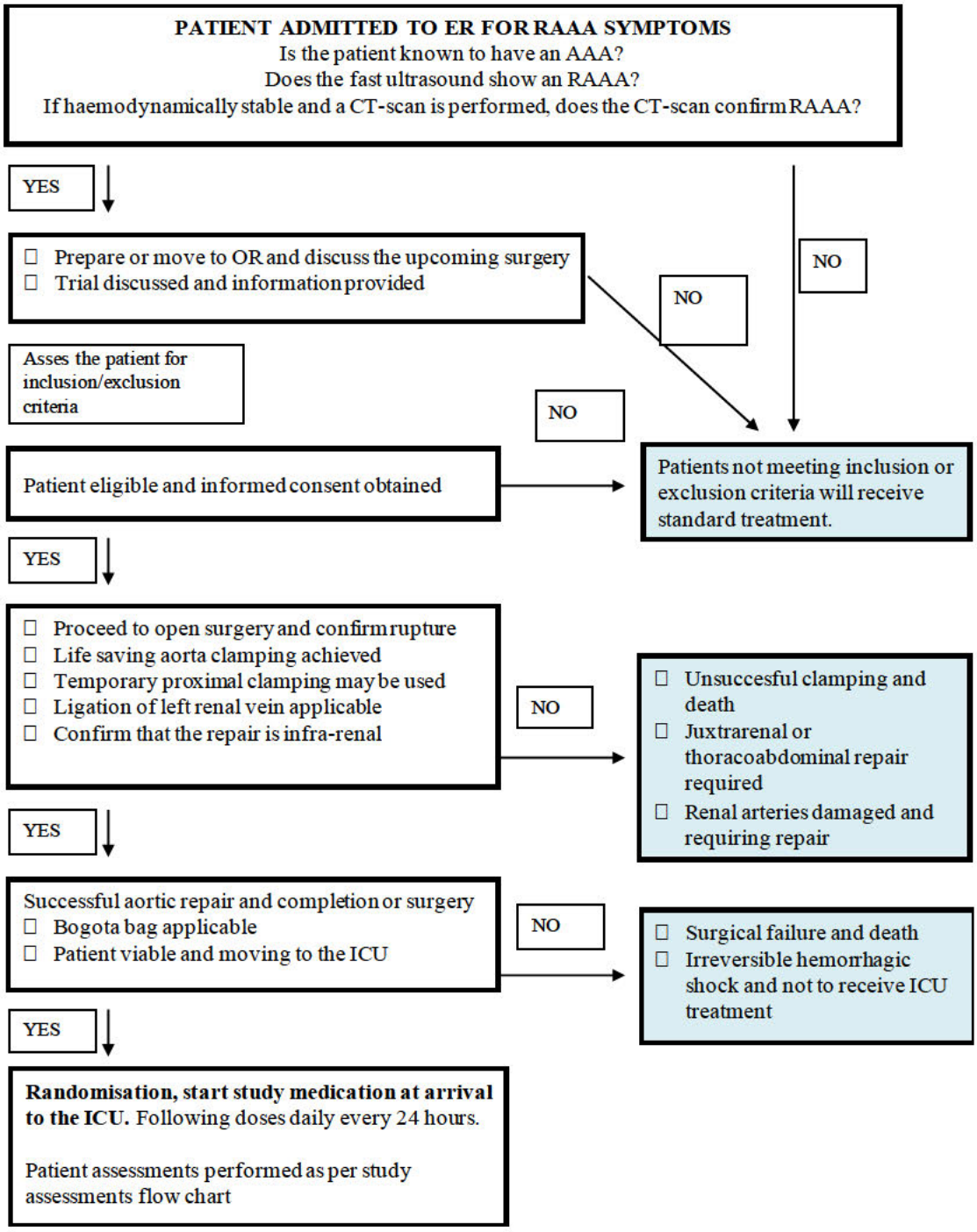
Statistical analysis, tables and patient data listings will be performed with SAS® version 9.4 or later for Windows (SAS Institute Inc., Cary, NC, USA).

18 References

Clinical Study Protocol (FP1CLO006), Final Protocol version 05 (16 April 2019), Faron Pharmaceuticals Ltd.

19 Appendices

19.1 Study flow chart



19.2 Study procedure flow charts

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, diagnosis and treatment of RAAA	X							
Medical History	X							
Inclusion / Exclusion Criteria	X							
Confirmation of all eligibility criteria		X						
Informed Consent +	X							
Demography	X							
Physical Exam (incl. PB, pulse)	X							
Time of onset of symptoms	X							
Hemodynamic collapse before ER	X							
Date and time of entry to ER	X							
Moving to OR for open repair	X							
Patient Randomisation (after consent & elig bility criteria confirmed)		X						
Hemodynamic collapse before clamping (yes/no)		X						
Proximal aortic clamp used(minutes/no)		X						
Check that renal arteries are intact		X						
Check that RAAA is infrarenal		X						
Check that the patient is still salvageable, no irreversible shock		X	X					
mRS		X						
SOFA Scoring ❖ (the worst obtained daily value should be used)			X	X 6-10am	X 6-10am	X 6-10am	X 6-10am	X 6-10am
Ventilator Free Days (VFDs)			X	X	X	X	X	X
Vital Signs; Temp, BP, HR (closest to 8am)		X		X 6-10am	X 6-10am	X 6-10am	X 6-10am	X 6-10am
Blood Biochemistry		X		X 6-10am	X 6-10am	X 6-10am	X 6-10am	X 6-10am
Haematology		X		X 6-10am	X 6-10am	X 6-10am	X 6-10am	X 6-10am
Intra-abdominal pressure (IAP)				X 6-10am	X 6-10am	X 6-10am	X 6-10am	X 6-10am
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 since Dose2	X 22h ±2h since Dose 3	X 22h ±2h since Dose 4	X 22h ±2h since Dose 5	X 22h ±2h since Dose 6
NAbs		X						

Concomitant Medications/Therapies	X	X	X	X	X	X	X	X
AE Recording (after obtained consent)		X	X	X	X	X	X	X
Major surgical outcome recording			X	X	X	X	X	X
Assessment of mortality and reason/diagnosis 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, assessements 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

∇ 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 D1 to D30, as applicable by standard clinical treatment at that point (therefore if a patient doesn't have an arterial line, no arterial blood sampling should be taken)

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	X	X	X	
Physical Examination	X	X	X	X	
Vital Signs; Temp, BP, HR (closest to 8am)	X 6-10am	X 6-10am	X 6-10am	X 6-10am	
Blood Biochemistry	X 6-10am	X 6-10am	X 6-10am	X 6-10am	
Haematology	X 6-10am	X 6-10am	X 6-10am	X 6-10am	
Intra-abdominal pressure (IAP)	X 6-10am	X 6-10am	X 6-10am		
MxA, CD73 and PIM	X 22h±2h since Dose 6	X 6-10am	X 6-10am		
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. Biochemistry, hematology, 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 pre-dose to D30, as applicable by standard clinical treatment at that point (therefore if a patient doesn't have an arterial line, no arterial blood sampling should be taken).

Flow Chart for Discharge Prior to D30 and After D30

ASSESSMENTS	Withdrawal	
	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	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	
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.

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

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