COVER PAGE FOR STATISTICAL ANALYSIS PLAN

Official Study Title: A Phase III Double-blind, Randomised, Parallel-Group Comparison of the Efficacy and Safety of FP-1201-lyo (Recombinant Human Interferon Beta-1a) and Placebo in the Treatment of Patients with Moderate or Severe Acute Respiratory Distress Syndrome

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Statistical Analysis Plan:

A Phase III Double-blind, Randomised, Parallel-Group Comparison of the Efficacy and Safety of FP-1201-lyo (Recombinant Human Interferon Beta-1a) and Placebo in the Treatment of Patients with Moderate or Severe Acute Respiratory Distress Syndrome

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1.3 Final	19APR2018		Updated Fig1, Table 3 and paragraph 3, Section 4.1 & Table 1, 3 not doses not 4

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CONTENTS.

1. Introduction

This is a phase III clinical study to investigate the efficacy and safety of FP-1201-lyo in patients with moderate or severe acute respiratory distress syndrome (ARDS).

FP-1201-lyo is a lyophilisate for solution for injection of interferon beta-1a (IFN) and is administered intravenously. Recombinant human IFN beta-1a is an approved treatment for patients with relapsing-remitting multiple sclerosis.

ARDS is a life threatening clinical disorder which follows a variety of severe lung insults such as pneumonia, aspiration of gastric contents, non-pulmonary sepsis and major trauma. It is characterised by injury to the endothelial barriers and alveolar epithelium of the lung with acute inflammation and protein-rich pulmonary oedema leading to acute respiratory failure.

Mortality rates across all severities range from approximately 20% to 40% but can be higher when associated with dysfunction in other organs. There are currently no approved pharmacological therapies for ARDS. Treatment is limited to supportive care.

This document describes in detail the framework for the analysis and reporting of all data obtained from this study prior to finalising the database and unblinding. Any changes made in the course of the evaluation and analysis of these data performed after the locking and unblinding the database will be documented and fully justified in the final integrated clinical report.

A single analysis at the conclusion of the study is planned with no formal interim investigations planned other than specified safety data reviews performed by an Independent Data Monitoring Committee (IDMC).

The Safety data reviews are performed at regular intervals and specific details of the requirements for these evaluations are documented in a separate Charter (see INTEREST Study IDMC Charter v1 0_16Oct2015 and INTEREST Study IDMC Charter_V 2.0 01Mar2018).

The main analysis itself is to be undertaken when all patient data collected up to 3 months post treatment is available (Day 90 or earlier in the event of withdrawal). However, subsequent supplemental follow-up analyses are planned after completion of a further 3 and 6 months observations to 6 months and 12 months post treatment (Day 180 and Day 360, respectively). These results will be added as addendums to the main Clinical Study Report. But, all efficacy and safety data available at Day 90 will also be analysed and reported in the main CSR, including all available data up to Day 180 and/or Day 360 where applicable.

This statistical analysis plan is based on FPCLI002 Protocol FINAL v 6.0 29Aug2017 and is in line with ICH E8 and E9 guidelines (Ref 1, 2).

2. Objectives

The primary objective is to investigate the efficacy of FP-1201-lyo through improvement of the clinical course and outcome at Day 28. Efficacy is based on a composite measure of both survival and the need for mechanical ventilation (VFDsurv) in patients with moderate or severe ARDS.

Further objectives concern investigation of Safety, Secondary Short term efficacy and Long term efficacy, Pharmacodynamics including immunogenicity, as well as Pharmacoeconomics.

Safety of FP-1201-lyo is investigated through patient assessment and adverse event reporting

Secondary efficacy objectives, assessed during the Short Term Follow Up period, include the assessment of mortality (all causes) at Day 28, with further ICU based efficacy evaluations of Organ failure, Renal support, Vasoactive support and Mechanical ventilation (including pulmonary function through gas exchange PaO2/FiO2 ratio) followed by Time spent in in intensive care unit (ICU) and Overall time spent in hospital.

Long term efficacy objectives, assessed during the Long Term and Extended Follow Up periods, include: investigation of survival (through Mortality Day 90, 180 and 360), requirement for mechanical ventilation (through Ventilation free survival), Quality of life (through EQ-5D-3L) and Organ functioning (through respiratory (FEV-1) and neurological (six minute walk test (6MWT)).

Pharmacodynamics objectives assessed during Short Term Follow Up period include the investigation of impact of FP-1201-lyo response through myxovirus resistance protein A (MxA), CD73 biomarker, Potential Inflammatory Markers (PIMs) and on neutralising antibodies to IFN beta-1a.

The Pharmacoeconomic value of FP-1201-lyo will be investigated through the total costs of standard treatment and care services used. These will be determined by application of unit costs to the key secondary efficacy outcome variables (Organ failure, Renal support, Vasoactive support, Mechanical ventilation and Stay in ICU/hospital).

A full description is provided in the protocol.

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3. Study Design

This is a multicentre, Phase III, double-blind, randomised, parallel-group comparison study of the efficacy and safety of FP-1201-lyo (10ug) compared with placebo in approximately 300 adult patients diagnosed with moderate or severe ARDS (see Figure 1).

After a careful screening process the aim is to obtain at least 272 evaluable patients for the assessment of efficacy.

Study centres are identified from Western Europe, with no more than 30 patients recruited from each. Patients are randomised to either FP-1201-lyo (10ug) or Placebo control in an allocation ratio of 1:1.

A stratified randomisation procedure is administered according to the Severity of the ARDS diagnosis (Moderate/Severe) and Country of investigational site. This enables control of the two factors which may impact the magnitude of the treatment effect.

Following satisfactory eligibility evaluations and successful randomisation, treatment consists of 6 doses of FP-1201-lyo 10 µg or Placebo control. Treatment is administered intravenously as a bolus, once per day, over 6 consecutive days. In order to be effective it is considered that administration of first dose must be within 48 hours of confirmed Moderate or Severe ARDS diagnosis.

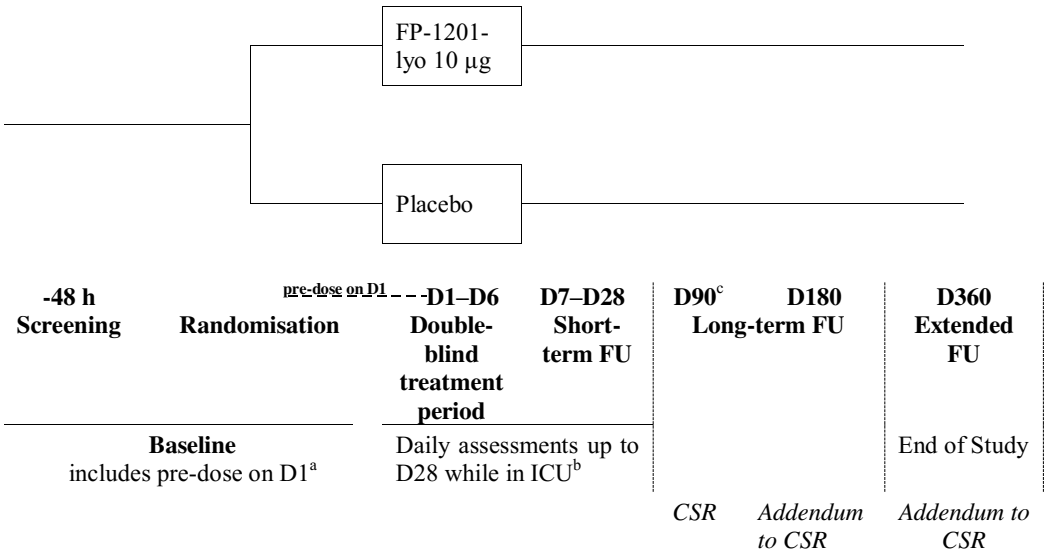
Patients are assessed daily while in the Intensive Care Unit (ICU) for up to a maximum of 28 days. This is called the Short Term Follow Up period. A complete set of evaluations are performed at the time of release from the ICU.

After leaving ICU (Day 28 or earlier), patients receive follow-up care with additional assessments performed at Day 90, 180 and 360. These are called the Long Term (Day 90, Day 180) and Extended Follow Up (Day 360) periods. Throughout (and indeed subsequently if required) the procedure for patient care follows normal hospital practice.

The schedule for all efficacy and safety assessments performed are outlined in Section 5 and summarised in Table 2.

No formal interim analyses are planned although an Independent Data Monitoring Committee (IDMC) will review on-going safety. Specifically all adverse events including any classified as serious will be reviewed on an unblinded basis. The IDMC will make recommendations to the Sponsor. The constitution, evaluation, recommendations and actual process details are given in a separate IDMC charter.

Figure 1 – Study Design



[a] *Not more than 48 hours may elapse between confirmation of moderate or severe ARDS during screening and administration of the first dose of study drug on D1. Randomisation can occur during screening or pre-dose on D1.*

[b] *Assessments are described in the Schedule of Procedures in Table 2 or the patient's last day in the ICU. These will be done on D28 or earlier, according to the clinical progress of the patient. If a patient leaves the ICU before D28, their survival status and other endpoints must be assessed on D28 (see schedule in Table 2).*

[c] *Can be visit or telephone contact.*

Abbreviations: CSR=Clinical Study Report; D=day; FU=follow-up; ICU=intensive care unit.

4. Analysis Sets

Three analysis sets (or subject populations) will be evaluated: The Full Analysis Set (FAS), Per Protocol Set (PPS) and the Safety Set (SS).

The Full Analysis Set (FAS) will consist of all randomised and treated patients who receive one or more doses and who provide post baseline data. Patients who receive the wrong treatment according to the randomisation schedule will be analysed according to the treatment that was assigned and not the treatment they actually received. This 'as randomised' population will be used for the analysis of the primary efficacy endpoint but a supporting 'as treated' population (sensitivity) analysis may also be included if sufficient patients are administered the 'wrong' treatment.

The Per Protocol Set (PPS) will consist of patients from the FAS but excluding those with major protocol deviations considered to be violations according to Section 4.1 below. A list of all

relevant situations which constitute major protocol violations and constitute reasons for exclusion from the PPS are specified in Section 4.1.

Patients who are to be included in and excluded from the PPS will be identified and listed following a Blind Data Review meeting prior to the database lock and unblinding at Day 90.

Statistical analyses for the primary and secondary endpoints will be performed using both the FAS and PPS (where appropriate). Although the FAS is considered of primary importance, the PPS will enable evaluation of the sensitivity and robustness of the estimates of the magnitude of the treatment effect

All other evaluations will involve the FAS population (i.e.: Demographic and baseline characteristics, Pharmacodynamics, Pharmacoeconomics).

The Safety Set (SS) will consist of all patients who receive at least one dose of study drug. All safety and tolerability evaluations will be based on this analysis set. Patients who receive the wrong treatment according to the randomisation schedule will be analysed according to the treatment actually received.

The SS population will be applied to all safety and tolerability assessments and analyses

Administration of the 'wrong' treatment applies to any of the 6 vials administered over the 6 day period. If a placebo randomised patient therefore receives at least one vial of active treatment they will be classified as actually treated with FP-1201-lyo. If a treated patient is however given one or more placebo vials they will still be classified as treated with FP-1201-lyo as long as one vial was correctly administered.

4.1 Protocol Deviations Considered to be Violations

Subject specific protocol deviations are defined and entered by Investigators, or CRAs, in the eCRF, and are graded as either minor or major.

But Violations are those protocol deviations defined by the Sponsor as being clinically important and may be in whole, or in part, a subset of the eCRF deviations. Any deviation considered by the Sponsor to be a ‘violation’ will lead to that patient being excluded from the PPS population. Table 1 defines these protocol deviations. To ensure that none of these deviations have been omitted, i.e. not captured by the Investigators and/or CRAs, Data Magik Ltd will programmatically interrogate the clinical study database and extract a listing of the events displayed in Table 1 below.

Furthermore, following the completion of PPD takeover from Gaea of the study management, all deviations in the eCRF database are being transferred and recorded in the PPD CTMS deviation tracker (except for Italian patients, who have not consented themselves). Deviations from these Italian patients will be tracked by the Sponsor using a compatible file to the PPD tracker. Prior to the Day 90 database lock, the deviations will be signed off by the Investigators, exported and sent to DML, and combined with the listing tracker produced from the DML database interrogation

process described above. This combined tracker report showing all deviations will be assessed by the Sponsor, study Medical Monitor and Data Magik Ltd statistical team at the population assignment meeting, and patients to be excluded from the PPS will be identified prior to the Day 90 database lock.

If patients fail to meet one or more of these criteria they will be excluded from the PPS.

Table 1: Protocol Deviations Considered to be Violations

Potential Violations	Detail/Criteria	Reason
Delayed or Incomplete treatment	Failure to treat within first 48 hours of diagnosis or receive less than 3 doses*	IMP needs to be taken within 48 hours of diagnosis and at least 4 doses are deemed necessary for clinical effectiveness
Mis- Dosing	Patient is given incorrect vials leading to 'mixed' treatments	May receive different treatment to the one assigned, or a combination of both treatments
Inclusion criteria	Failed one or more inclusion criterion	Data changed after dosing had commenced
Exclusion criteria	Failed one or more exclusion criteria	Data changed after dosing had commenced
Eligibility	Failed one or more eligibility criteria	Data changed after dosing had commenced
Temperature excursion	IMP must be stored at 2 – 8 ºC**	Active ingredient may be affected by temperature excursion.
Other reasons	Any Major Deviation considered by the Sponsor and Medical Monitor that might influence the effectiveness of the active compound	To ensure that the PPS contains only subject data which has not been 'clinically' compromised. Reasons for this decision will be recorded in a comments column on the assignment population spreadsheet during the population assignment meeting.

*Patients who die during the dosing period will not be excluded from the PPS.
** Individual temperature deviations outside 2-8 may have been accepted and the IMP considered valid for use based on IMP stability data. Those patients who have received an IMP with an temperature excursion, but accepted by the Sponsor, are not classified as Protocol Violations.

Consent:

Full details of the consent procedures are given in Section 9.6 of the protocol. In summary, whenever possible informed consent will be obtained from the patient. When this is not immediately possible due to the patient's condition, the informed consent can be given by a:

PerLR: Personal Legal Representative (e.g. relative, partner or close friend)

PrfLR: Professional Legal Representative (e.g. doctor not involved in the study)

Note: A separate consent will also be requested for patient's genetic sampling.

After PerLR or PrfLR, Investigators will attempt to obtain retrospective consent until Day 360, unless the patient's condition has precluded this (e.g. in case of death). If the patient refuses to give retrospective consent and the reason for withdrawal is 'retrospective consent not given' then all data for this patient will be removed from any analyses population group.

Withdrawal of consent: Patients may withdraw or be withdrawn (by the PerLR or PrfLR) from the study at any time and, any data collected up to the time of withdrawal can be included, unless consent for any use of the data has also been withdrawn. If not specified otherwise, data will be used up until the time of withdrawal.

Patient data excluded from any or all analysis populations because of a withdrawal of consent will also be reported in the population assignment record.

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5. Study Methods

The subject assessments performed during both the Short Term and Long Term/Extended Follow Up periods together with the timetable of events are summarised using only details relevant to the analyses provided. Precise details of all assessments performed on each study day are given in Section 6 of the protocol.

5.1 Schedule

The timetable of events are summarised in Table 2.

Table 2 Study Timetable and Assessment Overview (See protocol for full details)

	Screen-ing period	Double-blind treatment period Days 1-6			Short-term follow-up until D28 or discharge from ICU (whichever is earlier)				Long-term follow-up		Extended follow-up
	Baseline period				D7–D28						
Procedure	**48 h[a]**	**D1 pre-dose**	**D1**	**D2–D6**	**D7–D14**	**D15–D27**	**Last day in ICU[b]**	**D28[c]**	**D90[d] +14 days**	**D180 +14 days**	**D360 ±14 days**
Informed consent	X										
Medical history	X										
Demographic details	X										
Documentation of chest X-ray or CT scan	X										
Inclusion/exclusion criteria	X	X[e]									
Randomisation	X[f]										
Administration of study drug			X	X							
Survival				X - - - - - -	- - - - - -	- - - - - -	- - - - - -	- - - - - -	- - - - - -	- - - - - -	- - - - - - X
On mechanical ventilation? (Y/N)				X - - - - - -	- - - - - -	- - - - - -	- - - - - -	- - - - - -	- - - - - -	- - - - - -	- - - - - - X
In ICU/in hospital? (Y/N)				X - - - - - -	- - - - - -	- - - - - -	- - - - - -	- - - - - -	- - - - - -	- - - - - -	- - - - - - X
SOFA		X		X	X	D21	X	X [o]			
GCS (for SOFA and APACHE II)	X	X		X	X	D21	X	X [o]			
APACHE II	X [g]										
Renal and vasoactive support? (Y/N)		X		X - - - - - -	- - - - - -	- - - - - -	- - - - - -	- - - - - - X			

	Screen-ing period	Double-blind treatment period Days 1-6			Short-term follow-up until D28 or discharge from ICU (whichever is earlier)				Long-term follow-up		Extended follow-up
	Baseline period				D7–D28						
Procedure	**48 h[a]**	**D1 pre-dose**	**D1**	**D2–D6**	**D7–D14**	**D15–D27**	**Last day in ICU[b]**	**D28[c]**	**D90[d] +14 days**	**D180 +14 days**	**D360 ±14 days**
Blood sample: IFN beta-1a neutralising antibodies		X[h]					X	X			
Blood sample: MxA		X[h]		X	X						
EQ-5D-3L, FEV_1 and 6MWT		EQ-5D-3L[i]								X	X
PaO_2/FiO_2	X	X		X	X	X	X				
Blood sample: CD73 and PIM		X[h]		X	X						
Pharmacoeconomics							X	X			
Physical examination	X						X	X [o]			
Vital signs	X[j]	X		X	X	X	X	X [o]			
ECG		X			D7					X	X
Haematology, chemistry, urinalysis[k]	X[j]	X		X	X	X	X	X [o]			
Pregnancy test in women of childbearing potential	X										
Previous and concomitant medications and therapies	X[l]	X -X									
Adverse events	X[m]	X - X							X[n]	X[n]	X[n]
Blood sample: genetic analysis (requires separate consent)	X - - - - - - - - - - - - - 1 sample at any time while in ICU - - - - - - - - -X										

[a] *No more than 48 hours may elapse between confirmation of moderate or severe ARDS and administration of the first dose of study drug.*

[b] *These assessments will be done on the day the patient leaves the ICU, which will either be on D28 or earlier, according to the clinical progress of the patient. If the patient is still in the ICU on D28, the next visit or telephone contact will be at D90. If a patient leaves the ICU before D28, the survival status and other endpoints must be assessed on D28.*

[c] *D28 procedures apply for patients leaving the ICU before D28 and for patients withdrawing from the study before D28. For patients withdrawing from the study before D28 a sample should be taken for neutralising antibodies on the day they leave the ICU.*

[d] *D90 can either be a visit or telephone contact.*

[e] *Reconfirm inclusion/exclusion criteria before dosing, including that patient requires mechanical ventilation and is in the ICU (patients requiring ECMO after randomisation but before the first dose of IMP may still be included).*

[f] *Randomise after consent obtained and once eligibility criteria confirmed.*

[g] *Within 24 hours of ICU admission*

[h] *Within 1hour pre-dose.*

[i] *Baseline EQ-5D-3L to be obtained from relatives and checked later with patient.*

[j] *For APACHE II scoring.*

[k] *Samples should be taken in the morning between 04:00 and 10:00.*

[l] *Medicines and therapies in previous month.*

[m] *Adverse events will be recorded after informed consent is obtained.*

[n] *Deaths are reported as SAE*

[0] *if it is possible to be performed by the investigator*

Abbreviations: APACHE II=Acute Physiology and Chronic Health Evaluation; CD=cluster of differentiation; CT=computerised tomography; D=study day; ECG=electrocardiogram; ECMO=extra-corporeal membrane oxygenation; EQ-5D-3L=EuroQol 5-Dimensions 3-Levels questionnaire; FEV_1=forced expiratory volume in 1 second; GCS=Glasgow Coma Scale; ICU=intensive care unit; IFN=interferon; MxA=myxovirus resistance protein A; PaO_2/FiO_2=partial pressure of oxygen/fraction of inspired oxygen; PIM=potential inflammatory marker; SOFA=Sequential Organ Failure Assessment; 6MWT=6-minute walk test;.

5.2 Patient Status And Baseline Characteristic Assessments Prior To Treatment Start

Study specific patient eligibility assessments required prior to recruitment are recorded during Screening and/or at Pre-Dosing on Day 1 (Baseline).

5.2.1 Admission

At Admission to the ICU they include details of: Status including Intubation, Renal support, Body position and any required Vasoactive infused drug treatment.

These are then supported by a combined assessment of Acute physiology and Chronic health to derive an APACHE II score (0-71) to additionally classify the severity of the condition.

Demographics (Age, Race, Sex) are then supplemented with details of the Disease diagnosis and Aetiology supported by Imaging (Chest X-ray / CT scan) and Ventilation evidence (Gas exchange variables). Aetiology is categorised as: Pancreatitis, Trauma/Burns, Sepsis, Multiple Transfusion, Aspiration, Pneumonia or Other. If the cause is Sepsis then the site of infection is noted.

Following satisfactory completion of all the Inclusion/Exclusion criteria details (including a negative pregnancy test for females) Medical history (including any relevant previous and ongoing medical conditions) is recorded together with Prior medications (taken in the last 30 days but stopped before signing Informed consent) and a complete Physical examination (with predicted body weight).

Ongoing medications are recorded as Concomitant Medications (classified as either Bolus or Infusion) and reported accordingly if started prior to treatment dosing (Day 1). Any medication given with or after the first injection of study drug is also classified as a concomitant treatment.

Prior to the start of dosing on Day 1 the Patient status and Inclusion/Exclusion criteria are confirmed and all Medications are updated.

A series of Baseline safety assessments are then performed. These include: Safety laboratory tests (Biochemistry, Haematology, Urinalysis), Vital signs, 12 Lead ECG and Ventilation (Gas exchange). Specific variables measured are listed in section 5.8.

Baseline efficacy assessments performed are: the System Organ Failure SOFA score and Quality of Life (EQ-5D-3L) assessment. Details of the specific variable items measured are given in section 5.3.3.5 and 5.4.2 respectively.

Pre-dose blood samples are taken for pharmacodynamic baseline assessment. These include: Myxovirus Resistance Protein A (MxA), CD 73 biomarker, Potential Inflammatory Markers (PIMs). Also a sample for Anti Drug Antibodies (ADA) and Neutralising Antibodies (NAbs) to Interferon Beta-1a assessment will be taken. A tier based approach for the NAbs analyses will be used where NAbs will be assessed only if ADAs exists.

If all the study specific inclusion criteria are met then the patient is eligible for entry into the study. Screen failures are retained in the database, but only the patient screening number and reason for exclusion will be listed in the report.

5.2.2 Randomisation

Randomisation details, including details of the severity of the ARDS condition and any change in the condition are recorded on Day 1 of dosing. Drug compliance is not measured but a record of the daily infusion of the Study IMP (material number, date and time of administration) is maintained on Days 1-6. These data will be categorically summarised and individual details listed. Details of the construction (including block size) and application of the randomisation will be described in the Statistical Report. The severity of ARDS reported at Day 1 dosing will be used to assign patients to their respective groups (i.e. Moderate or Severe), irrespective of the stratification selected in the IWRS system.

5.3 Efficacy Assessments - Short Term Follow Up

Daily assessments are performed in the ICU for the evaluation of treatment benefit. This is the Short Term Follow Up period (Day 1 to Day 28).

Efficacy related assessments are predominantly performed as part of the Patient Status evaluation (see Section 5.3.1).

From these observations both primary and secondary efficacy endpoints to the end of the Short Term Follow Up period Day 28 can be derived. They include: Mortality (All causes), Mortality in ICU, Mortality in hospital, Days free of organ failure, of renal support, of vasoactive support and of mechanical ventilation together with the Number of ICU care free days and the Number of days in hospital. A combination of Mortality and the Need for mechanical ventilation is used to determine the primary efficacy outcome of the treatment (see Section 5.3.2).

Further efficacy evaluations involve assessment of the impact on body organs as a whole through the Sequential Organ Failure Assessment (SOFA) and individually through the need for Vasoactive support, Ventilation performance and Fluid balance and these are recorded separately (see Section 5.3.3).

The end of the Short Term Follow Up may be less than Day 28 if the patient is Discharged from the ICU or Withdrawn from the study. In either event a complete set of assessments identical to those performed daily and at the conclusion of the Short Term Follow Up (Day 28).

Further assessments following discharge from the ICU are then performed at Long Term and Extended Follow Up on Day 90 and Day 180 and Day 360 respectively (see Section 5.4).

5.3.1 Patient Status Assessments

The Patient Status assessments are performed on Days 1 (Pre-dose) then daily on Days 2 - 28 (Day 28 In or Out of ICU). At each visit patient details recorded are: Alive/Dead, Location of

death (ICU/Hospital), Date of death, Location if alive (ICU/Hospital), Requirement for mechanical ventilation, On renal support and Relative change in condition from yesterday.

At selected visits (Day 1 (Pre-dose), Day 27 - 28), Body positioning (except Day 28 if already left ICU), Vasoactive support and Concomitant medications and Other therapies are recorded.

Prior to Day 28 in the event of withdrawal an Early Termination is completed. In the event of discharge from the ICU a Last Day in ICU form is completed. Each includes a complete set of Patient Status evaluations.

In addition, at Day 28 patients who have been externally transferred and are no longer in the ICU complete details of the Total number of days spent free of Mechanical ventilation, free of Organ failure (SOFA score=0), free of Renal support and free of Vasoactive support. Totals for the entire short term follow up period are derived (see Section 5.9.4, Appendix 4). In addition, the total number of days spent in the ICU and the Hospital environment are also similarly derived.

5.3.2 Primary Efficacy - Ventilation Free Survival (VFDsurv)

The primary endpoint for treatment benefit includes Mortality and the Number of days free of Mechanical ventilation within 28 days among survivors as a composite measure (VFDsurv).

Mortality is patient death by Day 28. Ventilator-free days (VFDs) correspond to those days when unassisted breathing (UAB) is possible for a complete calendar day. For the initiation of the VFD count at least two consecutive calendar days of UAB are required.

The definition of UAB is given in the protocol and the actual VFDsurv and VFD scoring mechanisms are described in Section 5.9.4, Appendix 4.

5.3.3. Secondary Efficacy

Secondary efficacy assessments include: Mortality (All causes), Mortality in ICU, Mortality in hospital, Days free of Organ failure, of Renal support, of Vasoactive support and of Mechanical ventilation together with the Number of ICU care free days and the Number of days in hospital.

Additionally, Organ failure (SOFA score) and individual organ assessment through Vasoactive support, Ventilation performance and Fluid balance are also assessed.

5.3.3.1 Mortality Evaluations

Mortality is primarily assessed in the hospital at Day 28. All details are obtained from the daily assessment of Patient Status. Mortality is categorised as: Mortality (All causes), Mortality in ICU and Mortality in hospital.

The Mortality rate will be a proportion derived from the number of deaths up to Day 28 divided by the total number of eligible patients in the FAS patient population. The Mortality rate in the

ICU and Mortality rate in the hospital will be similarly calculated based on the location of the death.

Investigators are required to confirm mortality using the 'Death report' section of the eCRF. In the event of missing or insufficient information then patients are assumed alive and still 'at risk' at the time of assessment.

5.3.3.2 Days Free Of Mechanical Ventilation Evaluations

The Total number of days free of Mechanical ventilation is derived from the Patient Status report recorded on each day during the 28 day period. Patients who die during this period will be assigned a value of zero. Defined rules are specified in Section 5.9.4, Appendix 4.

The definition used by site staff for unassisted breathing (UAB) and 'being ventilator free for the whole of the calendar day' as recorded in the CRF is given in the protocol.

This variable is not the same as the calculated Ventilation Free Days (VFD) endpoint which contributes to the VFDsurv primary efficacy endpoint as it requires 2 consecutive calendar days of UAB. If there are fewer than 2 consecutive days of UAB then VFD is assigned the value zero.

5.3.3.3. Days Free Of Organ Failure, Renal Support, Vasoactive Support Evaluations

Patient assessment of Organ failure, Renal support and Vasoactive support is also recorded daily in the Patient Status record.

The Number of days free of Organ failure, Renal support and Vasoactive support is derived from this information using defined rules and algorithms specified in Section 5.9.4. Patients who die during this period will be assigned a value of zero.

A patient will be defined as being free of organ failure when the SOFA score is zero. However, as organ failure is only assessed at Day 21 and Day 28 after Day 14 a scoring scheme will be used to derive the total number of days.

This is:
If Day 21 and Day 28 are both zero then 50% of the days between Day 14 and Day 21 and 100% of the days between Day 21 and Day 28 will be assumed to be zero.
If Day 21 is non-zero and Day 28 is zero than 100% of the days between Day 14 and Day 21 will be assumed to be non-zero and 50% of the days between Day 21 and Day 28 will be assumed to be zero.
Finally if Day 21 is zero and Day 28 is non-zero then 50% of the days between Day 14 and Day 21 will be assumed to be zero and 100% of the days between Day 21 and Day 28 will be assumed to be non-zero (also see Section 5.9.4.2, Appendix 4).

The need for Renal support or for Vasoactive support is defined in the protocol.

5.3.3.4. Length Of ICU 'Care Free' Stay/Hospital Stay

Patient stay in the ICU and Hospital setting is also recorded daily in the Patient Status record. The Number of ICU care free days and the Number of days in hospital is derived from this information using defined rules and algorithms specified in Section 5.9.4, Appendix 4. Again patients who die during this period will be assigned a value of zero.

5.3.3.5 Sequential Organ Failure Assessment (SOFA)

Organ failure status is assessed using the SOFA score. This assesses six organ systems and the score ranges from 0-24 with a score of zero indicating no organ failure (see Protocol for the scoring mechanism).

The scores are based on the worst daily values recorded for: Hypotension/Use of vasopressors (Cardiovascular score), PaO2/FiO2 (Respiratory score), Platelets (Coagulation score), Bilirubin (Hepatic score), Creatinine (Renal score) and Glasgow Coma Scale (GCS) (CNS score).

The SOFA score is assessed pre-dose on Day 1, then daily up to Day 14 and then at Day 21 and Day 28 In or Out of the ICU or at withdrawal (Early Termination).

The Last observation performed whether at Day 28 or earlier will be derived.

The change from baseline (Day 1 Pre-dose) will be calculated.

The values for each contributing variable in the scoring mechanism are recorded by the site staff in Patient Status record of the EDC system and the total scores are derived programmatically according to the algorithm specified in the protocol.

5.3.3.6. Individual Organ Assessments

A number of separate assessments are performed to assess the functioning of individual body organs including: Cardiovascular, Pulmonary and Renal.

5.3.3.6.1 Cardiovascular Function

The need for Vasoactive support is recorded daily in the Patient Status (Days 1 (Pre-dose) then daily on Days 2 - 28 (Day 28 In or Out of ICU) at the Medications update and specific details are recorded in the Concomitant infusion vasoactive medications record.

The Last observation performed whether at Day 28 or earlier will be derived.

The Number of days free of Vasoactive support is derived from this information using defined rules and algorithms specified in Section 5.9.4, Appendix 4.

5.3.3.6.2 Pulmonary Function

Ventilation assessments are recorded daily (Days 1 (Pre-dose) then daily on Days 2 - 28 (Day 28 In or Out of ICU).
Gas exchange measurements are performed. Measures include: Fraction inspired oxygen (FiO2), Partial pressure arterial oxygen (PaO2), PaO2/FiO2 ratio, PEEP together with a Baro-trauma classification (Yes/No). The PaO_2/FiO_2 ratio change from baseline will used to assess pulmonary function.

The Last observation performed whether at Day 28 or earlier will be derived.

The change from baseline (Day 1 Pre-dose) will be calculated. However, Fraction inspired oxygen (FiO2), Partial pressure arterial oxygen (PaO2), PaO2/FiO2 ratio and PEEP may be measured at Day 1 dosing and, in this case, these values will be utilised for the change from baseline calculations.

Additional measurements of Peak inspiratory pressure, Plateau pressure, Mean airway pressure, Respiratory rate and Tidal volume are collected at Screening and Day 1 (Pre-dose) only.

At Day 1 Pre-dose and also at Day 28 (In or Out of ICU or earlier in the event of Early Termination) the severity status of ARDS will be classified as Mild (except Pre-dose/Day 1 dosing), Moderate, Severe or Death (Table 3) and numerically rated from 1-4 respectively.

Improvement is defined as a decrease in the severity score at the Last observation performed (Day 28 or earlier if withdrawn), No change is a zero change score and Worsening an increase in the severity score.

Both the Severity status and Change score (from Investigator CRF Day 1 dosing) classifications will be categorically summarised, and post Day 1 classifications will be calculated as follows:

Table 3: ARDS Severity Classification Post Day 1

ARDS Severity	Variable	Criteria
Mild -1	PaO2/FiO2 Ratio	200 mmHg < PaO2/FIO2 ≤ 300 mmHg
Moderate-2	PaO2/FiO2 Ratio	100 mmHg < PaO2/FIO2 ≤ 200 mmHg
Severe-3	PaO2/FiO2 Ratio	PaO2/FIO2 ≤ 100 mmHg
Death-4	(Patient Status)	Yes/No

5.3.3.6.3 Renal Function

Fluids are monitored on a daily basis with the total input and output recorded (Day 1-28 / Last Day in ICU) and Fluid balance calculated (Input-Output).

The Last observation performed whether at Day 28 or earlier will be derived.

The change from baseline (Day 1 Pre-dose) will be calculated.

5.3.3.7 Information from Externally Transferred Patients

Observations recorded by site staff for patients who are externally transferred between Day 7 and Day 28 include: Total number of days spent in an ICU/Hospital, free of mechanical ventilation, free of organ failure, free of renal support or free of vasoactive support plus death date.

As this is a subset of patients these will only be numerically summarised. However, these data may contribute to the 'Days free' or 'Days spent' variable derivations and survival indicator (see Section 5.9.4, Appendix 4).

5.3.3.8 Other Observations In The ICU

Other observations recorded during Days 1-28 include Concomitant medications taken and any notable Procedures, Interventions, Surgeries sand Diagnostics. These data will be categorically summarised and listed respectively.

5.4 Efficacy Evaluations - Long Term/Extended Follow Up

Long term follow up is performed first at Day 90 and then Day 180 after discharge from the ICU. This is followed by a further Extended follow up at Day 360. In the event of Early termination (on or before Day 28) no Long term follow up is performed.

Efficacy is assessed through Patient status assessments performed at Day 90, Day 180 and Day 360 with Respiratory and Neurological functioning and Quality of life (EQ-5D-3L) assessed at Day 180 and Day 360.

5.4.1 Patient Status Assessments

The Patient Status assessment records: Alive/Dead, Location of death (ICU/Hospital), Date of death, Location if alive (ICU/Hospital), Requirement for assisted ventilation at Day 90, 180 and 360 in a similar manner to those performed during Short Term Follow Up in the ICU.

These data will be categorically summarised.

5.4.2 Quality Of Life Evaluations

General assessment of health is performed through a quality of life questionnaire (QOL). The EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L) is administered at Day 1 Pre-dose, Day 180 and Day 360.

An EQ VAS score (ranging from 0-100) is measured (0= Worst imaginable health state, 100= Best imaginable health state) together with sub scores for Mobility, Self-care, Usual Activities, Pain/Discomfort and Anxiety/Depression. Each sub score ranges from 1 to 3 with 1 representing the best case and 3 the worst case.

The change from baseline (Day 1 Pre-dose) will be derived.

5.4.3. Respiratory and Neurological Assessments

5.4.3.1 Respiratory Function

Respiration through the FEV-1 test is only assessed at Day 180 and Day 360 (and only if able to attend the hospital). This is a general test of pulmonary function. The FEV-1 is the volume exhaled as % of Forced Vital Capacity in 1 second.

Baseline measurement is not appropriate. These data will be numerically summarised.

5.4.3.2 Neurological Function

The Six-minute Walk Test (6MWT) is performed at Day 180 and Day 360. It evaluates global and integrated responses of all systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood and neuromuscular units and muscle metabolism.

The distance travelled over the 6 minute period on a flat, hard surface is recorded together with other potentially contributing factors. (Specific details of the procedure are given in the protocol Appendix II).

The test itself is performed according to the Respiratory Society/American Thoracic Society guidelines (Ref 11). The guidelines recommend that each test should be performed twice and the best result should be used. According to these guidelines this is usually the second result as it includes a 'learning effect'.

Details are recorded Pre-test, during the test and also post test for both Test One and Test Two.

Pre-test evaluations assess the Overall patient suitability to undergo the test (Absolute/Relative contraindications, ECG findings, Medication prescribed, Co morbidities present), Vital signs (Walking limitations, Systolic/Diastolic blood pressure, Heart rate, Oxygen required with flow rate and Peripheral capillary oxygen saturation(Sp02) and any other debilitating Symptoms (Dyspnoea and Fatigue as measured by the modified Borg scale (0-10)).

During the test the number of stops made by the patient and those requested by the Assessor are recorded.

After each test the Vital signs and any debilitating Symptoms are again recorded together with the Total distance walked (m) and the conditions under which the test was undertaken.

The Total distance walked (m) during Test One and Test Two on Day 180 and Day 360 will be numerically summarised together with the furthest distance walked during Tests One or Test Two. During this study, many patients have only performed the test once. Therefore, when only the first result is available this will also be used as the best result.

Baseline measurement is not appropriate. All other data will be numerically/categorically summarised as appropriate.

5.4.4 Study Completion / Unblinding

After completion of the Short Term Follow Up period and as part of the Long Term/Extended Follow Up assessment period the completion of a Study Completion form is mandated at the end of study Day 180 or Day 360. Either the date of Withdrawal (if before Day 180 or Between Day 180 and Day 360) is recorded or the date of the End of Long Term Follow Up or Extended Follow Up is given.

All details of the reason for termination (including the primary reason) are given: Screen Failure, Protocol Violation, Non-Compliance, Lost to Follow-up, Retrospective Consent Not Given, Other Withdrawal of Consent, Investigator Decision, Death, Adverse Event (Non-Serious), Serious Adverse Event (Non-Fatal) or Other.

Any Unblinding performed (Yes/No) with Date of unblinding and Reasons are also recorded.

5.4.5 Exploratory Efficacy - Ventilation Free Survival At Day 90

A protocol defined (Section 3.2.4) exploratory assessment of efficacy Ventilation Free Survival at Day 90 will be summarised. As daily assessments are not performed between completion of the Short Term Follow Up (Day 28) and Day 90, VFDsurv at Day 90 will be categorically classified as Dead, Alive-On Ventilator, Alive-Breathing Unassisted and summarised.

5.4.6 Secondary Efficacy - Mortality At Day 90

Mortality (All causes) up to Day 90 will be derived from the recorded Date of Death (recorded as part of the Patient Status).

Investigators are also required to confirm mortality using the ‘Death report’ section of the eCRF. In the event of missing information, then patients are assumed alive and still 'at risk' at the time of assessment.

The cause of death detailed in the Death Report will be categorically summarised.

The date of death will also be used to produce Kaplan-Meier estimates and these will be displayed in plots to assess survival curves and median survival times. The number of patients 'at risk' at each assessment time will be superimposed. Information from the date of randomisation and for the entire follow up period will be taken into account. Patients who withdraw, are lost to follow-up, or are alive without the event occurring since the last follow-up will be considered right censored.

Mortality up to Day 180 and Day 360 will be evaluated as part of the Long Term and Extended Long Term Follow up assessments, respectively, and included as addendum reports (see Section 6.1.6 and 6.1.7).

5.5 Pharmacoeconomic Evaluations

The total cost of treatment and care whilst patients are confined in the ICU (up to Day 28) will be derived from key individual patient efficacy measures and assigned unit costs for each measure.

UK Unit costs are considered representative and are given in Table 4.

Specific efficacy measures used are: Days free of organ failure, Days free of renal support, Days free of vasoactive support, Days free of mechanical ventilation, Number of ICU-free days, Number of days spent in hospital.

Individual patient need for these services will be determined in terms of days of use (subtracted from 28 for 'days free' or actual for 'days spent') and these will be multiplied by the daily costs to derive a total cost burden for each service and overall services.

Table 4: Treatment And Care Costs Per Patient in the UK

Support Service	Unit	Cost (£)
Organ Failure Support (SOFA)	Per Day	TBC
Renal Support	Per Day	TBC
Mechanical Ventilation	Per Day	TBC
Vasoactive Support	Per Day	TBC
Stay In ICU	Per Day	TBC
Stay In Hospital	Per Day	TBC

TBC: To Be Confirmed

The unit costs per patient will be provided to DML by the Sponsor prior to analysis, and will be based on the most current (2018) financial data available in the UK. Data for other countries may be displayed at a later date.

These data will be numerically summarised overall patients by Treatment group (FP-1201-lyo/Placebo) and Severity of ARDS (Moderate/Severe). However, to expedite the finalisation of

the Day 90 CSR, these summaries will be presented with the Day 180 and/or Day 360 long-term follow up reports and not at Day 90.

5.6 Pharmacodynamic Including Immunological Evaluations

Blood samples are taken on a number of occasions during confinement in the ICU during the Short Term Follow Up (Day 1-Day 28) to assess a range of Pharmacodynamic effects.

5.6.1 Anti Drug Antibodies (ADA) and Neutralising Antibodies to Interferon Beta-1a (NAb)

The immunological response to FP-1201-lyo is assessed through monitoring of neutralising antibodies to IFN beta-1a on Day 1 Pre-dose and at Day 28, the Last day in ICU or Early termination (if earlier). NAb can interfere with the biological and clinical response to treatment. Anti-Drug Antibodies (ADAs) are determined first and if present, the NAbs are also determined. In case a fit for purpose ADA assay for FP-1201-lyo cannot be established, only the NAb assay will be done.

The Last observation performed whether Day 28, Last Day in ICU or Early termination will be derived.

The Positive/Negative classifications will be categorically summarised.

5.6.2 Myxovirus Resistance Protein A (MxA)

MxA are interferon-induced GTPases and mediate an antiviral response to a broad range of viruses. MxA activity is one of the best markers for IFN beta bioactivity and is often used to monitor the IFN beta treatment in Multiple Sclerosis patients. MxA levels are thus induced by the IFN beta treatment and possibly by the underlying disease. This response is measured on Day 1 Pre-dose and daily thereafter until Day 14 in the ICU.

The Last observation performed whether Day 14 or earlier will be derived.

The change from baseline (Day 1 Pre-dose) will be calculated.

5.6.3 Biomarkers - CD73

CD73 is an ecto-5'-nucletidase controlling the dephosphorylation of adenosinemonophosphate (AMP) to adenosine. The key rationale of FP-1201-lyo (IFN beta-1a) treatment is that FP-1201-lyo is a potent inducer of CD73 expression. Thus, the FP-1201-lyo treatment induces the CD73 expression on cell surfaces resulting in increased adenosine levels and the subsequent restoration of the endothelial barrier function. CD73 levels are assessed at Day 1 Pre-dose and daily thereafter until Day 14 in the ICU.

The Last observation performed whether Day 14 or earlier will be derived.

The change from baseline (Day 1 Pre-dose) will be calculated.

5.6.4 Biomarkers For Inflammation (PIM)

Cytokines, chemokines and growth factors are secreted by several different cell types to stimulate or dampen the immune response during the different stages of infection or trauma. These biomarkers of inflammation are measured on Day 1 Pre-dose and daily thereafter until Day 14 in the ICU and could provide information on the disease severity and progression and also on treatment response. Specifically, PIM samples will be analysed from serum using the Bio-Rad multiplex kit Bio-Plex Pro™ Human Cytokine 27-plex Assay for the assessment of the following 27 potential biomarkers: FGF basic, Eotaxin, G-CSF, GM-CSF, IFN-γ, IL-1β, IL-1ra, IL-2, IL-(4 -10), IL-12(p70), IL-13, IL-15, IL-17, IP-10, MCP-1 (MCAF), MIP-1α, MIP-1β, PDGF-BB, RANTES, TNF-α, VEGF.

The Last observation performed whether Day 14 or earlier will be derived.

The change from baseline (Day 1 Pre-dose) will be calculated.

Summary of PIM results will be included in the D90 CSR, but the full analyses, which will be of an exploratory nature, will be reported separately at Day 180 and/or Day 360.

5.7 Pharmacogenetic Evaluations

A blood sample for pharmacogenetic analysis is obtained during the study.
Each DNA sample extracted from the patient blood samples will be subjected to targeted resequencing of six genes (*NT5E, IFNAR1, IFNAR2, MCM2, ANGPT2, RASSF3*). For this, a custom amplicon panel, AmpliSeq, was designed and produced by Illumina. The amplicon panel covers the whole gene region (exons, introns and UTRs) and 3 kb up- and down-stream. The raw data obtained will be subjected to quality control and preprocessing steps before subsequent mapping to a human reference sequence. Mapped reads will undergo variant calling (SNPs and indels) to identify and annotate the variants found in the samples. Based on the metadata produced, the samples may then be divided into groups to study which variants (if any) are enriched in a particular group of samples. Further, the annotation utilizing publicly available data sources provides predictions on the possible impact a variant has on the protein structure, levels and functions.

The final exploratory genetic analyses are still to be decided and a separate SAP describing these analyses will be produced and the results will be reported at Day 360, for the patients who have given genetic informed consent.

5.8 Safety Evaluation Endpoints

Subject safety is monitored throughout the period of confinement in the ICU (Short Term Follow Up: Day 1-28). Specific evaluations include: Vital signs, 12-lead ECG, Physical examination, Adverse events and Laboratory safety tests (Biochemistry, Haematology, Urinalysis). Specific timings of assessments are specified but unscheduled recordings may be performed as necessary.

As part of the Long/Extended Term Follow Up period thereafter safety is assessed as part of the ongoing standard of patient care (Day 90, 180 and 360). In addition to a Patient Status assessment any notable Adverse events are recorded.

Detailed descriptions and definitions of all safety variables are described in the protocol.

5.8.1 Vital Signs

Vital signs are recorded at Day 1 (Pre-dose), then at selected visits (Day 2 - 28 (In/Out of ICU), Last day in ICU) and in the event of withdrawal, at Early Termination. The Last observation performed will be derived and identified.

On each occasion measurements involve recordings of: Blood pressure (systolic/diastolic), Mean arterial pressure, Heart rate and Body temperature and Total respiratory rate. Procedural details are given in the protocol.

The change from baseline (Day 1 Pre-dose) will be calculated.

5.8.2 Twelve Lead ECGs

Twelve Lead digital ECG recordings are performed at Day 1 (Pre-dose) then on Day 7.

On each occasion measurements involve recordings of: Ventricular rate, PR, PQ Interval, QRS Duration, QTc and Categorised Normal/Abnormal result. Procedural details are given in the protocol.

The change from baseline (Day 1 Pre-dose) will be calculated.

ECGs are also performed on Days 180 and 360 prior to the Six-minute walk tests to ensure patient safety during that evaluation. The ECG data from these visits will be listed only.

5.8.3 Physical Examination

Physical examinations are recorded at Day 1 (Pre-dose), then at the Last day in ICU and Day 28 (Out of ICU) and in the event of withdrawal, at Early Termination. The Last observation performed will be derived and identified.

This includes the major body systems: General appearance, Ear, nose and throat, Eyes, Respiratory, abdomen, Urogenital, Musculoskeletal, Neurological, Lymph nodes and Skin.

At screening Height is also measured to enable calculation of the Predicted body weight (PBW: For men: 50 + 0.91(height in cm – 152.4, For women: 45.5 + 0.91(height in cm – 152.4).

5.8.4 Adverse Events (AEs)

Adverse events are defined as any untoward medical occurrence subsequent to administration of an investigational product that does not necessarily have a causal relationship with the treatment. (For a full definition refer to the protocol).

AE collection starts from signing the Informed Consent and continues until the end of the D28. AEs possibly related to the study drug (by investigator) and/or leading to death are collected until the end of Extended Follow Up period (Day 360). AEs will be categorised according to those that occur during the period of confinement in the ICU (up to Day 28) and those that occur thereafter during the Long Term/Extended Follow Up period.

Adverse events starting on or after the first treatment dose are defined as Treatment Emergent Adverse Events (TEAEs). Any event starting before the first dose of study drug on Day 1 will be identified as a Pre-Treatment Sign or Symptom (PTSS). Any event starting before the first dose of study drug on Day 1 but subsequently worsening will also be defined as a TEAE.

All events will be coded using the MedDRA dictionary. The actual description of the AE will be matched, as closely as possible, with the Lower Level Term (LLT) in the dictionary.

Related AEs are any AE reported as possibly related or related to the study drug according to the investigator. Any events with missing relationship to study drug will be tabulated as related. AE intensity is reported as mild, moderate or severe. Any events with missing intensity will be tabulated as severe. If a subject has an AE which changes in severity this will be recorded as a separate event. Serious adverse events (SAEs) are classified as described in the protocol. If a subject has more than one AE and at least one is considered drug-related, the subject will be included as having a drug-related AE. Similarly, if a subject has more than one AE and at least one is considered severe, then the subject will be included as having a severe AE.

All SAEs are reported and then processed separately according to standard pharmacovigilance practice.

Patient survival is assessed as part of the regular Patient Status assessment. The location at the time of death (ICU or hospital) is recorded. All deaths are recorded as AEs and SAEs up to and including Day 360.

As part of the Death report (Day 180 or Day 360) the cause of death is categorised as: Acute Coronary Syndromes, Arrhythmia, Brainstem Death, Bleeding, Cardiac Failure, Cerebral Event, Multiple Organ Failure, Pulmonary Embolus, Respiratory Failure, Sepsis, Withdrawal of Treatment (e.g. removal of mechanical ventilation) or Other.

5.8.5 Laboratory Safety

Laboratory safety assessments (haematology and chemistry and urinalysis) are performed at Day 1 (Pre-dose), then at daily during intensive care (Day 2 - 28 (In/Out Of ICU), Last day in ICU) and in the event of withdrawal, at Early Termination. The Last observation performed will be

identified and derived. Additional laboratory assessments may be performed if required (Unscheduled).

All laboratory results are obtained from the hospital local laboratory. In view of the variability between the participating laboratories with respect to assays performed, units used and normal ranges applied the actual numerical values will only be used to determine within patient changes at the time of assessment.

However, the laboratory values will also be classified by the Investigator as Out of range (Not clinically significant), Out of range (Clinically significant) or Out of range (Clinically significant and an Adverse event).

The specific Haematology laboratory variables measured are: Haemoglobin, Haematocrit, Erythrocytes, MCV, Platelets, Leucocytes and Differential counts of: Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes.

The specific Biochemistry laboratory variables measured are: Albumin, Creatine kinase, Creatinine, Glucose, Triglycerides, Urea, Bilirubin, Total protein, Alkaline phosphatase, AST, ALT, Lactate, Sodium, Potassium, Bicarbonate, Calcium (total calcium corrected for albumin level) and Chloride.

Variables for Urinalysis are: pH, Protein, Glucose, Ketones, Bilirubin and Blood.

5.9 Data Definitions And Conventions

Details of how all the available data are managed under particular situations are specified. This is to ensure consistency within the analysis and reporting. Aspects of data definition and conventions, data derivations and strategies in particular circumstances are detailed.

5.9.1 Definition Of Baseline

The baseline assessment is considered to be the Day 1 Pre-dose unless the assessment is only performed at Screening.

In the event of the site needing to repeat the Screening Safety laboratory tests the last available 'valid' pre-dose assessment will be entered in the EDC system and used in all cases as the baseline value.

5.9.2 Conventions For Assessment Visits

During confinement in the ICU for up to the required 28 days all visit assessments are performed on a daily basis and therefore as scheduled. Therefore, there is no requirement to allow for 'Visit Windows'.

However as subsequent follow up at Day 90, 180 and 360 could occur after discharge from hospital there is the potential to miss the target date. The acceptable margin of +14 days is permitted for D90 and D180 assessments, and ± 14 for D360 assessments.

Given the margin permitted these data will be presented according to the visit section they were completed in the CRF. Therefore, there is no requirement for programmatically re-slotting results due to the visit 'windows'.

In the event of any Unscheduled assessments, for example in the case of additional Safety laboratory assessments or Vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing AEs) these will only be included in the report listings. They will not be included in the construction of the report summaries or analyses.

As only the most relevant laboratory assessment is reported on a daily basis in the EDC system there is no requirement for evaluation of the applicability of any Unscheduled assessments in relation to identifying and using the first valid observation for a given assessment time. Unscheduled assessments will however be presented in listings. Invalid laboratory values from haemolysed, mishandled, insufficient quantities, or other conditions for samples therefore will not be entered into the EDC or used.

5.9.3 Conventions For Managing Unblinded Data

In the event of unbinding, all patient data (with the exception of safety data) will be reviewed as part of the Blind Data Review to assess the potential impact and biasing of the statistical analysis before inclusion. All such data will be included in listings and flagged appropriately.

5.9.4 Data Derivations

Data Derivations, Section 5.9.4 is presented in Appendix 4.

5.9.5 Strategy For Assessing Sources Of Variability

Both the Country and Severity of ARDS are considered major sources of variability and potentially influencing factors on the magnitude of the treatment effect. Both are included as strata in the randomisation process. All analyses will include these as factors in statistical models or classification strata for hypothesis tests in order to ensure the precision of estimates obtained.

Recruitment of patients to individual sites within each of the countries is likely to be highly variable. However, although the process of pooling of patients within country should produce a more uniform distribution this will be monitored. In the event of low recruitment in some countries then country pooling strategies may need to be investigated in order to minimise variability. Decisions regarding pooling will take place at the Blind Review.

The impact of patient variability on the Severity of ARDS (Moderate, Severe) will also be explored.

As the adjustment for covariates increases the precision of estimates in proportion to correlation with outcome measure, demographic and other baseline patient data will also be assessed as additional sources of potential variability. Identified variables will be included in the statistical models to evaluate the sensitivity and robustness of the magnitude of the treatment effects determined in the main analyses.

Sources of variability will be assessed at the Blind Data Review prior to database lock at Day 90 and subsequent unblinding. These will include but not limited to the following baseline variables: age, race, sex, Apache score, SOFA score, disease diagnosis, aetiology (including presence/absence of shock), country, PaO2/FiO2 ratio, plateau pressure, tidal volume, PEEP, mode of ventilation, respiratory rate, vasoactive drug use, renal support, patient position, co-morbidities from MH coding, season (quarter), study stage, arterial pressure, arterial pH, weight (BMI), renal/liver biochemistry (creatinine, CK, AST, ALT). If other variables are assessed during the blinded review, these will be described in the Day 90 statistical analysis report.

5.9.6 Strategy For Missing Data

No biases resulting from missing data are anticipated and, as a consequence No imputation of any missing values at any of the assessments performed is planned.

However, to allow for patient attrition or any changes to the scheduled patient assessments as a consequence of the treatment response a 'Last observation performed' assessment will be derived for specific Short term efficacy (Ventilation assessment, System Organ Failure (SOFA), Cardiovascular, Pulmonary and Renal function), Pharmacodynamic (IFNß ADA & Nab, MxA, CD73, PIM) and Safety variables (Vital signs and Laboratory assessments). This approach will use the last available non-missing post baseline value.

6. Statistical Methods

6.1 General Considerations

All data derivations, manipulations and reporting procedures will use SAS v9.4 in a Windows 7 operating system environment.

For all evaluations, data will be described and analysed according to Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Country (1-8) and where appropriate Assessment period (Screening, Day 1 Pre-Dose, Short Term Follow Up (Day 1-28 ICU based), Long Term Follow Up (Day 90, Day 180) and Extended Follow Up (Day 360)) will be included. In addition, other endpoints summarising overall response are derived and analysed (e.g.: VFDsurv - the survival plus days free from mechanical ventilation composite).

All the data collected are to be summarised, and the descriptive statistics produced will account for the nature and distribution of the data collected. For continuous variables, data will be presented as number (n), mean, median, standard deviation, and range. For discrete variables data

will be presented as frequencies and proportions (as appropriate) and the denominator will be the number of patients available in the relevant population.

6.1.1 Null Hypothesis

The Null Hypothesis throughout the investigations is that there is no difference between treatment (FP-1201-lyo) and placebo (Control).

That is: H_0: $\mu_1 = \mu_2$, where H_0 = the null hypothesis, μ_1 = the mean/proportion of treatment group 1, and μ_2 = the mean/proportion of treatment group 2.

Each hypothesis test or statistical model therefore constructed compares the obtained results with the distribution under the null hypothesis and assesses the likelihood that chance or random processes alone were responsible.

Two tailed directionality (H_0: μ_1 ^= μ_2: Treatment superior or Placebo superior) is to be assessed.

The primary efficacy endpoint is considered to be a composite, Ventilation Free Survival (VFDsurv). This comprises of Mortality and Number of ventilation free days.

6.1.2 Sample Size And Power Estimation

Sample size and power estimations were performed at the outset to determine the required size of this investigation. These were detailed in the protocol (see Section 8.10).

It was decided that a total of 272 evaluable patients would be required to demonstrate a clinically relevant difference between the active treatment and placebo control with a two-tailed significance level of 0.05 and 90% power using a non- parametric test comparison (Mann–Whitney U-test). PASS software (Version 11; NCSS LLC, Kaysville, UT, USA) was used for all calculations.

The clinically relevant difference at the end of the Short Term Follow Up (Day 28) was comprised of:

- A mortality rate of 30% in the placebo control group and 15% in the FP-1201-lyo group.
- 20% of patients who survive in the placebo control group have zero ventilator-free days.
- A mean difference of 3.0 days in ventilator-free days (FP-1201-lyo - Placebo control) (VFD=0 with deaths assigned Score=0).

Calculations assumed multinomial distributions and an overall attrition rate of 9% (5% drop-out, 4% non evaluable). This resulted in a recruitment requirement of 300 patients.

However, the attrition rate will be monitored during the course of the investigation. If it proves to be in excess of 9% then recruitment process will continue until 272 evaluable patients are available.

6.1.3 Multiplicity Of Testing

In view of the number of statistical tests employed to assess the secondary efficacy endpoints measured, a hierarchical approach will be employed which ranks the endpoints in order of importance to control for the multiplicity of testing.

The pre-specified hierarchy for the secondary endpoints is:

1. Mortality (All-cause) at Day 28
2. Mortality in ICU at Day 28
3. Mortality in hospital at Day 28
4. Overall Mortality at Day 360

The process will involve declaring statistical significance down to the first non-significant endpoint (based on a two-sided significance level of 0.05). However, all p-values will be presented and those that are ≤0.05 but below a non-significant endpoint in the hierarchy will be considered as nominally significant but not formally significant.

Mortality during the follow up period (Day 90, 180 and 360) is considered secondary and included as part of the Kaplan-Meier survival analysis.

All other statistical hypothesis testing applied and p-values generated during the exploratory or safety evaluations will only be used as indicators of potential interest or concern requiring clinical expert commentary.

A two-sided significance level of 5% (0.05) will be used throughout, although in line with standard practice this may be relaxed to 10% when investigating potential model interactions.

6.1.4 Interim Analyses

A single analysis at the conclusion of the investigation is intended. No interim analyses will be performed. However, in order to monitor patient safety a Sponsor-Independent Data Monitoring Committee (IDMC) was formed and regularly convened according to the requirements of the IDMC Charter to assess the accumulating data.

The safety data provided to the IDMC will be unblinded by a study Independent Statistician to enable identification of treatment group and simplify the medical review process.

IDMC data summaries and listings required for review purposes are given in the IDMC Charter.

The primary analysis is considered to be once all patients have completed Day 90 (or earlier in the event of withdrawal). Once these data become available the evaluation of the efficacy endpoints that relate to the Short Term Follow Up at 28 days and the Long Term Follow Up at Day 90, together with all available safety will reported. Efficacy endpoints associated with later time points (Day 180 and Day 360) will be analysed subsequently and any accumulating safety data re-presented where appropriate.

6.1.5 Blind Data Review

Prior to the Day 90 database lock and unblinding a blinded review of the entire data up to Day 90 (and any available post Day 90 data) will be performed.

This will serve several purposes. It will enable identification of questionable values, potential outlier patients and potential missing data which may require ratification. It will enable identification of potential sources of variability (see Section 5.9.5) and it will enable assessment of the structure of the table shells. Patient populations will then be assigned by the Sponsor according to the definitions in Section 4 of this SAP.

For evaluation of the suitability of the table shells a 'dummy' randomisation will be used which has a known structure to prevent mistaking for the actual randomisation code.

6.1.6 Long Term and Extended Follow Up Periods (Day 180, Day 360) Addendum Reports

All data collected up to and including the first 3 months follow up (Short Term Follow Up (Day 1-28 in ICU), Long Term Follow Up (Day 90) together with the primary analyses will be included in the main clinical study report (CSR).

However, all patients will be followed up for another 3 months (Long term Follow Up (Day 180, i.e. Day 90 – Day 180)) and then a further 6 months (Extended Follow Up (Day 360, i.e. Day 180 – Day 360). Assessments performed at Day 180 and Day 360 will include: Patient Status (including Mortality at Day 360), Quality of life, Respiratory functioning (FEV-1), Neurological functioning (6MWT), Patient Completion, Unblinding, Additional AEs and Death reporting. All are considered efficacy variables, except any additional AE reports, and as such will involve patients from the FAS population. Medications, deviations and comments data will also be followed up after the Day 90 visit at both Day 180 and Day 360.

Separate or addendums to existing tables and listings will be generated. However, all available data up to and including Day 360 will be presented with the main report at Day 90 and Day 180 addendum report.

Details of the outputs required (including summary tables, analyses and listings) are given in Section 7.4.

6.1.7 Pharmacogenetic Evaluations

The potential influence of patient genotype on the treatment outcome will be performed and reported separately to the main analysis through a specific pharmacogenetic evaluation.
The final genetic analyses are to be decided and those results will be reported separately at Day 360.

6.2 Statistical Analyses

6.2.1 Overall Study Patient Group

Basic information regarding the sample of patients obtained to represent the ARDS population will be summarised. This includes: Disposition, Major Protocol Violations and Deviations, Patient Status and Baseline Characteristic Assessments Prior to Treatment Start, and Randomisation. Details are given in Section 7.2.1

6.2.2 Baseline Treatment Group Comparability

No formal statistical comparisons of the treatment groups at baseline will be performed as this serves only to assess the randomisation procedure. A descriptive clinical evaluation of the representativeness of this population sample will be described in the Clinical Study Report (CSR).

6.2.3 Efficacy Assessments - Short Term Follow Up

Assessments performed during Days 1 to 28 during confinement in the ICU are considered of critical importance.

6.2.3.1 Patient Status Assessments

All Patient Status assessments performed on Days 1 (Pre-dose) then daily on Days 2 - 28 (Day 28 In or Out of ICU), at Early Termination or Last Day in ICU will be summarised (See Section 7.2.3.1).

6.2.3.2 Primary Efficacy Analysis - Ventilation Free Survival (VFDsurv)

Ventilation Free Survival (VFDsurv) is a composite measure of Mortality and the Number of days free of Mechanical ventilation (VFD) within 28 days among survivors. The Ventilation Free Days (VFD) count requires two consecutive calendar days of unassisted breathing (UAB) and the precise definition is given in Section 5.9.4.1.

The combination of time to event measure (mortality) with a longitudinal measure (VFD) follows methodology for scoring and analysis proposed by Finkelstein and Schoenfeld (Ref 3).

According to the scoring scheme definition and derivation rules described, higher scores indicate better response with the possible integer scores range from -1 to 28.

VFDsurv scores derived will be numerically summarised (excluding means and standard deviations) according to Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall according to the FAS population. Separate supporting summaries by Country will also be included.

A non-parametric analysis will be performed as the data distribution is non normal and negatively skewed. This will involve a generalised Wilcoxon rank sum based stratification test which assigns ranks within strata and compares two treatments within strata (Van Elteren hypothesis test) (Ref 4). The Treatment groups are (FP-1201-lyo/Placebo) with stratification variables Severity of ARDS (Moderate/Severe) and Country (1-8). Statistical significance (p-values) obtained will be displayed with the numerical summaries.

The analysis will primarily use the FAS population but this will be repeated using the PPS group as supporting information.

Summary statistics only will be presented for severity of ARDS subgroups and by country, but will not include non-parametric analysis p-values.

Other baseline characteristic variables potentially contributing to sources of variability may be included in further sensitivity analyses and these will be investigated during the blinded review as described in Section 5.9.5.

6.2.4 Secondary Efficacy Analysis

Other efficacy variables analysed include: Mortality rates, Days free of Mechanical ventilation (actual days not VFD calculated days), Days free of Organ Failure, Renal Support And Vasoactive Support, Length Of ICU 'Care Free' Stay/Hospital Stay, Sequential Organ Failure Assessment (SOFA) and Other Individual Organ Assessments

6.2.4.1 Mortality Analysis

The Mortality rate is principally assessed during the Short Term Follow Up in the hospital at Day 28. However, the mortality rates occurring within the ICU and in the hospital will be calculated separately using the location of the death. The Overall mortality rate irrespective of location will be analysed.

The observed Mortality rates (with 95% Confidence Intervals (Clopper Pearson)) for each Treatment group (FP-1201-lyo and Placebo) and the Treatment difference (FP-1201-lyo - Placebo) will be displayed using categorical summarises (Alive/Dead) according to Severity of ARDS (Moderate/Severe) and Overall according to the FAS population. Separate supporting summaries by Country will be included.

The binary mortality endpoint outcome (Alive/Dead) will be modelled using logistic regression applied (Ref 6) to the FAS population. The model will include Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Country (1-8) as factors.

Homogeneity of treatment effect will be assessed by calculating ORs and associated confidence intervals by ARDS severity and by country and displaying these in a Forest Plot (log scale).

The analysis will primarily use the FAS population but this will be repeated using the PPS group as supporting information.

Other baseline characteristic variables potentially contributing to sources of variability may be included in further sensitivity analyses.

6.2.4.2 Days Free Of Mechanical Ventilation Analysis

The actual Total number of days free of mechanical ventilation (not the derived VFD scores which require additional conditions of UAB to be met) will be numerically summarised (excluding means and standard deviations) according to Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall. Separate supporting summaries by Country will be included.

These endpoints will be analysed using the same methods as for the primary efficacy variable, VFDsurv, using the Van Elteren hypothesis test as the distribution is likely to be non-normal and negatively skewed by patients who are assigned scores of zero (0) in the event of death.

6.2.4.3 Days Free Of Organ Failure, Renal Support And Vasoactive Support Analysis

Totals derived will be numerically summarised and analysed as described in Section 6.2.4.2 above.

6.2.4.4 Length Of ICU 'Care Free' Stay/Hospital Stay Analysis

Totals derived will be numerically summarised and analysed as described in Section 6.2.4.2 above.

6.2.4.5 Sequential Organ Failure Assessment (SOFA) Analysis

Total scores and Change from baseline scores (Day 1 Pre-dose) assessed daily up to Day 14 and then at Day 21 and Day 28 (In or Out of the ICU) or Early Termination, together with the derived Last observation performed will be numerically summarised according to Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall using the FAS population. Separate supporting summaries by Country will be included.

The contributing Cardiovascular, Respiratory, Coagulation, Hepatic, Renal and CNS organ sub scores will be similarly presented.

The Total SOFA score at the Last observation performed will be analysed using an Analysis Of Covariance (ANCOVA) model (Ref 8) this will use change from baseline as the response variable and will include Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Country (1-8) as fixed effect factors. The Baseline value will also be used as a covariate term in the model.

Model assumptions of normality and constant variance will be investigated and if necessary an alternative model or data transformation will be substituted.

Model estimates (LS means and a 95% confidence interval for the treatment difference) will be presented. Homogeneity of treatment effect will be assessed by obtaining the difference in LS means together with 95% confidence intervals for the categories of ARDS severity using the ANCOVA model with the addition of a treatment by ARDS severity interaction term and displaying these in a Forest Plot.

Sub scores will not be analysed.

6.2.4.6 Individual Organ Assessments Analysis

6.2.4.6.1 Cardiovascular Function

Vasoactive support assessments recorded daily (Days 1 (Pre-dose) then daily on Days 2 - 28 (Day 28 In or Out of ICU) will be will be categorically summarised (Yes/No) with the derived Last observation performed, by Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall for each assessment time using the FAS population.

6.2.4.6.2 Pulmonary Function

Ventilation assessments recorded daily (Day 1 (Pre-dose/Day 1 dosing) then daily on Days 2 - 28 (Day 28 In or Out of ICU) will be numerically summarised (with the derived Last observation performed) using the actual values and change from baseline values by Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall for each assessment time using the FAS population. Separate supporting summaries by Country will be included.

Each of the gas exchange variables measured will be reported but the PaO_2/FiO_2 ratio change from baseline will used to assess pulmonary function.

In addition, an Analysis of Covariance (ANCOVA) model, similar to the Total SOFA scores in Section 6.2.4.5 will include the PaO_2/FiO_2 ratio change from baseline value as the response variable at the Last observation performed assessment time.

Homogeneity of treatment effect will be assessed as for the SOFA score.

The Severity status and Change score classifications derived over the period of confinement within the ICU will be categorically summarised according Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and overall using the FAS population.

The derived overall Change score classification (Improved, No Change, Worsened) will be analysed using the Cochran-Mantel-Haenszel hypothesis test including Severity of ARDS and Country as stratification variables. Statistical significance (p-value) overall will be displayed with the categorical summaries. Summary counts will be presented by severity of ARDS (Moderate/Severe).

6.2.4.6.3 Renal Function

Fluid balance monitored at Baseline (Days 1 (Pre-dose) and then daily on Days 2 - 28 (Day 28 In or Out of ICU) will be numerically summarised (with the derived Last observation performed) using the actual values and change from baseline values by Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall for each assessment time using the FAS population.

6.2.4.7 Information from Externally Transferred Patients

Observations recorded by site staff for patients who are externally transferred between Day 7 and Day 28 will be numerically summarised as this is applies to only a subset of patients.

These data will be added to the 'Days free' endpoint scores and 'Length of stay' variables as appropriate for specific patients according to derivations specified in Section 5.9.4, Appendix 4.

6.2.4.8 Other Observations In The ICU

Other notable Procedures, Interventions, Surgeries and Diagnostics which are recorded as free text during confinement in the ICU will be listed.

6.2.5 Efficacy Evaluations - Long Term/Extended Follow Up

Assessments performed at Day 90 and Day 180 are considered Long term follow up and those at Day 360 an Extended follow up. These will only involve the FAS population.

6.2.5.1 Patient Status Analyses

The Patient Status assessments of efficacy performed at Day 90, 180 and 360 will be categorically summarised by Treatment group and Severity of ARDS and Overall using the FAS population.

Details include: Alive/Dead, Location of death (ICU/Hospital), Date of death, Location if alive (ICU/Hospital) and Requirement for assisted ventilation. All are summarised and listed.

6.2.5.2 Quality Of Life Questionnaire Analyses

The EQ-5D-3L is performed at Day 1 Pre-dose, Day 180 and Day 360. The EQ VAS score and sub scores will be numerically summarised for actual values and change from baseline by Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall for each assessment time using the FAS population only, although this sample will exclude any patients who did not survive to Day 180 or Day 360. Separate supporting summaries by Country will not be included.

The EQ VAS score will be analysed using an Analysis Of Covariance (ANCOVA) model as described for Total SOFA scores in Section 6.2.5.5. A separate analysis will be performed at each assessment time (Day 180 and Day 360) although p-values for inferential purposes will not be presented.

Sub scores will not be analysed.

6.2.5.3 Respiratory And Neurological Function Assessment

6.2.5.3.1 Respiratory Function (FEV-1) Analyses

FEV-1 measured at Day 180 and Day 360 will be numerically summarised using actual values by Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall for each assessment time using the FAS population only. Again this group will only include survivors at the time of assessment. Separate supporting summaries by Country will not be included.

The FEV-1 will be analysed using an ANCOVA model (as for the Total SOFA scores in Section 6.2.5.5 but excluding the baseline covariate).

6.2.5.3.2 Neurological Function (6MWT) Analyses

6MWT distances recorded at both Day 180 and Day 360 will be numerically summarised using actual values by Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall for each of the performed tests (Test One/Test Two). They will also be summarised according to the furthest distance walked during Test One or Test Two as recommended by the 6MWT guidelines (Ref 11). Separate summaries by Country will not be included.

These will involve patients from the FAS population who survive up to the time of assessment.

In line with the guidelines the furthest distance walked during the two tests will be analysed using an ANCOVA model (similar to the Total SOFA scores in Section 6.2.5.5 excluding the baseline covariate). As described in Section 5.4.3.2, in cases where only one result is collected this will also be used as the best result (furthest distance walked). The value of inclusion of additional Pre-Test covariates such as Walking limitations, Supplemental Oxygen use, SP02, Dyspnoea or Fatigue will be explored.

In addition, the distance walked during Test One will also be performed as a supplemental analysis in case there is a disproportionate number of patients across the two treatment groups who refuse or who are unable to perform the second test and which may lead to inconsistent inclusion of a possible 'learning effect'.

As the 6MWT is likely to only be performed in what is effectively a selective subgroup of patients (i.e.: those who survive) the results will be assessed in conjunction with the mortality rates in the two treatment groups. The LS mean and the 95% confidence interval for the treatment difference in those LS means will therefore only be presented Overall.

All other measures will only be summarised.

6.2.5.4 Study Completion / Unblinding

Long term and Extended follow up completion details reported at Day 180 and Day 360 respectively will be categorically summarised by Treatment group, Severity of ARDS and Overall for the FAS population according to whether the Patient has withdrawn (Yes/No) and the Primary Reason for termination. All other reasons will be listed.

A supporting Unbinding (Yes/No) categorical summary will be provided and all details listed.

6.2.5.5 Ventilation Free Survival At Day 90 Analyses

Ventilation Free Survival at Day 90 will be classified as Dead, Alive-On Ventilator or Alive-Breathing Unassisted and summarised according to Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall. Separate supporting summaries by Country will be included.

A Cochran-Mantel-Haenszel hypothesis test including the stratification levels will be used to compare the two treatment groups. Statistical significance (p-values) obtained for the Overall group will be displayed with the categorical summaries.

6.2.5.6 Mortality At Day 90

Overall mortality through to Day 90 (and subsequently to Day 180 and Day 360) will be displayed using Kaplan Meier survival plots and analysed using the logrank test.

Kaplan Meier product limit estimators of survival, together with median survival times (with 95% confidence intervals) for each treatment group will be presented.

The distributions will be compared for differences in rates between the two treatment groups (FP-1201-lyo/Placebo) with the stratified logrank hypothesis test (stratified by ARDS severity and country). The adjusted hazard ratio, obtained by fitting a Cox PH model containing both ARDS severity and country as factors in the model will be presented with 95% confidence intervals

Sensitivity analysis may be performed to assess the impact of censoring in the event of missing data due to withdrawal due to adverse events, efficacy, investigator decision or loss to follow up and also due to withdrawal of consent (as detailed on the Day 180/Day 360 Patient Status CRF page).

Homogeneity of treatment effect will be assessed by obtaining hazard ratios and associated confidence intervals by ARDS severity and by country and displaying these in a Forest Plot (log scale) using the Cox PH model with the addition of treatment by ARDS severity and treatment by country interaction terms.

Mortality at Day 180 and Day 360 will be similarly assessed as part of the Addendums for the Long Term and Extended Follow Up Reports, respectively (see Section 6.4).

6.2.6 Pharmacoeconomic Analysis

Numerical summaries of overall costs and according to cost item for the UK will be by Treatment group (FP-1201-lyo/Placebo) and Severity of ARDS (Moderate/Severe) using the FAS population. NB: Separate summaries by other countries may be included later.

A cost-effectiveness analysis (Ref 9) to compare treatment with FP-1201-lyo to standard care (Placebo control) will involve an Analysis Of Variance (ANOVA) model. The total individual patient cost of treatment whilst in the ICU will be the response variable and Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Country (if available) will be included (without interactions) as fixed effect factors.

The total cost will be logarithmically transformed prior to analysis as the data distribution is likely to be truncated and positively skewed. The model fit and assumptions (particularly residuals) will be carefully assessed to ensure that the model is adequate and therefore provides reliable estimates.

Resulting model parameters for Treatment (FP-1201-lyo and Placebo) will be back transformed (exponentiated) to obtain geometric mean estimates (including 95%CI) of the total cost of each treatment and similar transformation of the treatment difference (FP-1201-lyo - Placebo) will allow expression of the difference in costs as a ratio (FP-1201-lyo relative to Placebo (%)) with 95% confidence limits.

In the event of model failure a non-parametric bootstrap procedure (Ref 10) will be substituted which involves repeated resampling from the available data to obtain estimates of the mean treatment costs together with 95% confidence intervals (using 2.5 and 97.5 percentiles from the resulting distribution).

A supplemental Incremental Cost Effectiveness Ratio (ICER) plot may also be presented for each Treatment group using the primary efficacy endpoint (VFDsurv) vs total cost of treatment for each individual patient.

This quadrant plot will identify both increasing and decreasing utility of the treatment cost with those of treatment efficacy

As discussed, these summaries will be presented with the Day 180 and/or Day 360 long-term follow up reports.

6.2.7 Pharmacodynamic Endpoints Including Immunological Markers Analysis

IFN Beta-1a ADA and NAb is measured at Day 1 Pre-dose and at Day 28 (or Early Termination or last day in ICU), MxA, CD73 and other biomarkers such as PIMs are measured on Day 1 Pre-dose and then daily until Day 14 in the ICU. These will be summarised categorically or

numerically (with the derived Last observation performed) according to Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall using binary classifications (Positive/Negative) or the actual values and change from baseline for the FAS population depending on the type of variable. Separate supporting summaries by Country will be included.

For the categorical variable, the observed proportions with 95% Confidence Intervals (Clopper Pearson) at Day 28 (or Early Termination) will be analysed and displayed. The binary classification will involve the Cochran-Mantel-Haenszel hypothesis test with Severity of ARDS and Country as stratification variables.

For numeric variables the change from baseline at the Last observation performed will be used for the purpose of analysis. This will involve an Analysis Of Covariance (ANCOVA) model as for the Total SOFA scores in Section 6.5.5 and will include change from baseline value as the response variable.

As the PIMs biomarkers are considered exploratory, further sensitivity analyses may also be performed and the results will also be presented and justified in any supporting statistical reports.

6.3 Safety Evaluations

Specific evaluations include: Vital signs, Twelve lead ECG, Physical examination, Adverse events and Laboratory safety tests (Biochemistry, Haematology, Urinalysis). Interval or Categorical data summaries (as appropriate) for the SS population will be used to assist clinical evaluation. No formal statistical analyses will be performed. All safety summaries will be presented according to Treatment group and Severity of ARDS (Moderate/Severe) but there will be no grouping by Country. Details are given in Section 7.3.

6.4 Addendums Long Term and Extended Follow Up Efficacy And Safety Reports

Data collected at Days 180 and 360 encompassing the Long Term and Extended Follow Up periods (Day 90 to Day 180, and Day 180 to Day 360, respectively) will be summarised separately and issued as addendums to the Clinical Study Report (CSR). Details are given in Section 7.4. Table shells are given in Appendix 5 and Appendix 6.

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7. Presentation

7.1 General Information

All data described in Section 5 and 6 will be presented in tables, figures and listings. Detailed ‘shells’ to accompany this section are located in Appendix 1 to 6.

All tables will be displayed as courier new font size 8pt, in a landscape orientated A4 Word document. Solid lines will be provided beneath all column headings and after the last row of data. Each summary table will be supported by individual subject data listings (Section 7.5).

All demographic and safety data summaries will be produced for the FAS and SS populations respectively according to Treatment group (FP-1201-lyo, Placebo).

Efficacy, Pharmacodynamic and Pharmacoeconomic data analyses and summaries will be produced for the FAS population according to Treatment group (FP-1201-lyo, Placebo), Severity of ARDS (Moderate/Severe) and Country (1-8). The denominator for all categorical data summaries will be the number of patients available in the population.

Graphical displays will be provided according to Treatment group (FP-1201-lyo, Placebo) Overall and by Severity of ARDS (Moderate/Severe).

A Consort diagram will be used to classify the number of patients enrolled: Assessed for eligibility, Excluded/Included, Randomised, Treated, Followed up after ICU confinement and Analysed (by population) overall patients and by Treatment group and according to Severity of ARDS (Table 14.1).

The following described tables, figures and listings will be included in the statistical report.
Note: All listings will be output with the original Day 90 report, and the Day 180 and Day 360 addendums including all relevant additional data, e.g. adverse events and medications reported after Day 90, together with any other additional safety and efficacy data. Tables and figures will be output for the main report once 300 patients have completed short term follow up at Day 28, and long term follow up at Day 90. Additional tables and figures will be output after locking long term follow up data at Day 180, and subsequently after locking data reported at the extended long term follow up at Day 360. The Day 180 and Day 360 report addendums will be displayed according to Appendix 5 and Appendix 6 table shells.

7.2 Output Formats

7.2.1 Overall Study Patient Group

7.2.1.1 Disposition

Overall study disposition details at Day 90 will be summarised by Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Country (1-8) and Overall for all patients considered for inclusion. This categorical summary will include details of the number of patients Screened, Randomized no medication, Randomized, Treated in the ICU (Day 1-28), Completed the Short Term Follow Up Day 7, Short Term Follow Up Day 14, Short Term Follow Up Last Day in ICU, Short Term Follow Up Day 28 and Long Term Follow Up (Day 90) and also the numbers actually assigned to each of the analysis sets. Additionally, all available data will be used to indicate the number and percentage of patients who have completed Day 180 and/or Day 360 at this time. Supporting listings will detail the reasons for screen failure (Tables 14.1.1). Tables 14.1.1 will be re-presented both on completion of the long term visit at Day 180 (including all available Day 360 data), and subsequently for the extended long term visit at Day 360 in the Addendum Day 180 and Day 360 reports.

The number of patients completing each of the study periods, with all reasons for discontinuation, will also be displayed.

The disposition will also include information on the proportion of patients who Completed treatment (Days 1-6 of dosing) and those who Discontinued treatment (Less than 6 and also less than 4 days dosing) in the Day 90 report (Table 14.1.2), together will all available discontinuation data for patients who have reached or would have reached Day 180 and/or Day 360. This table will be re-presented in the Day 180 Addendum report and include the number and percentage of subjects who completed Long Term Follow Up at Day 180 and those who discontinued before Day 180 with reasons for discontinuation together will all available patient completion/discontinuation data at Day 360. This summary will be repeated by country (Tables 14.1.2). Tables 14.1.2 will be represented once all Day 360 data has been locked.

Additionally, any potential Investigator unblinding details or death reports recorded at Days 180 or 360 will be listed separately in the respective Addendum reports.

Furthermore, study informed consent and genetic sampling informed consent and associated dates and times are listed by treatment group and subject.

7.2.1.2 Protocol Deviations, Violations And Investigator Comments

Listing 16.2.1.4 will display all protocol deviations recorded in the eCRF and which were then subsequently transferred to the PPD CTMS tracker (which also contains site specific deviations), together with a similar tracker to be supplied by the Sponsor from Italian sites. The listing will identify country, site, patient, treatment group, description and date of the deviation, relevant Visit name, any action taken and, 'if relevant' whether the deviation was considered significant (yes/no) and the source (PPD, Faron, DML). The Sponsor, study MM and Data Magik Ltd statistical team will review these combined trackers and additional listing sets produced by Data Magik Ltd as described in Section 4.1. Table 14.1.3 summarises the assignment of each patient to their population group (Screen failure, RNM, PPS, FAS, safety).

Investigator comments will be listed by treatment group and subject.

7.2.1.3 Patient Status And Baseline Characteristic Assessments Prior To Treatment Start

Assessments performed on Admission to the ICU, including time from admission to first dose of IMP, time from intubation and mechanical ventilation to first dose of IMP, and patient status (requiring renal support, in the prone position, receiving vasoactive drugs), are summarised according to Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall according to the FAS population. Separate supporting summaries by Country will be included (Tables 14.1.4).

Demographics (Age, Race, Sex, APACHE II score) (Tables 14.1.5), plus Disease diagnosis and Aetiology (Tables 14.1.6 and 14.1.7) are similarly summarised using the FAS population, together with all Medical history past conditions (Table 14.1.8.1) and Medical history ongoing conditions (Table 14.1.8.2).

Medical history is classified using the Medical Dictionary for Regulatory Activities (MedDRA) terminology matching verbatim reported text to the Lower Level Term according to System Organ Class (SOC) and Preferred Term (PT). Prior and concomitant medications will be similarly summarised using the World Health Organization Drug Dictionary coding system (WHODD) according to ATC levels 2 and 4.

Prior medications are those taken in the last 30 days but stopped before signing Informed consent and before injection of the first dose of treatment (Table 14.1.9). Concomitant medications (classified as either Infusion or Bolus) (Tables 14.1.10.1 and 14.1.10.2) are those starting between Screening and Day 28, or start before the first dose of study IMP but then continue after this point. Concomitant vasoactive medications are recorded separately and will be summarised (Table 14.1.11) and indicated in the supporting listings. Tables 14.1.10.1, 14.1.10.2 and 14.1.11 will be re-presented in the Addendum report at Day 180 and Day 360, and will include any additional medication reported after Day 90, and Day 180, respectively.

Details of pregnancy testing for woman of childbearing potential will be presented in a summary table according to Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall according to the FAS population (Table 14.1.12).

Inclusion and exclusion criteria will be defined in Part 1 and individual patient responses listed in Part 2 of Table 14.1.13, by severity and country according to the FAS population.

Physical examination at Screening will be presented as the number and percentage of patients for each body system categorised by the Investigator as ‘normal, abnormal NCS, abnormal CS, or not done’ according to Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall according to the FAS population (Table 14.1.14).

Patient status on Day 1 Pre-Dose will be summarised in a similar manner to the physical examination summary (Table 14.1.15).

All other assessments (efficacy, safety, pharmacodynamics) performed at Baseline (Screening and/or Day 1 Pre-dose) which are subsequently repeated during treatment and follow up will be summarised and reported with the appropriate data collected over time.

7.2.1.4 Randomisation

Randomisation, Severity of the ARDS condition, Changes in the condition and Individual daily infusion details during Days 1-6 will be summarised according to Treatment group. The scheduled treatment and actual treatment received with any 'miss' randomisations and the assigned analysis set will also be indicated. The record of the daily infusion of the Study IMP (material number, date and time of administration) maintained on Days 1-6 will also be included.

Details of any unblinding (reported at Day 180 and Day 360 follow up assessments) will be included in the addendum reports (Table 14.1.16).

7.2.2 Baseline Treatment Group Comparability

Group comparability will be discussed in the final Clinical Study Report (CSR).

7.2.3 Efficacy Assessments - Short Term Follow Up

7.2.3.1 Patient Status Assessments

All Patient Status assessments performed will be summarised according to Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall (Tables 14.2.1).

Patients no longer in ICU (Externally Transferred Patients) will also be separately summarised.

7.2.3.2 Primary Efficacy Analysis - Ventilation Free Survival (VFDsurv)

VFDsurv scores derived will be numerically summarised (excluding means and standard deviations) according to Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall. Statistical significance overall (Van Elteren p-values) will be displayed with the numerical summaries. Both FAS and PPS group analyses will be given (Table 14.2.2.1.1). Table 14.2.2.1.1 will also display secondary efficacy variables in the same manner, including Ventilation Free Days (VFD), Days Free of Organ Failure, Days Free of Renal Support, Days Free of Vasoactive Support, Days Free of Mechanical Ventilation, Number Of ICU Care Free Days, Number of ICU days and Number of Days In Hospital.
A frequency distribution (Table 14.2.2.2), together with Box and Whisker plots (Figures 14.2.1) of the VFDsurv scores will be presented by Treatment group and by Severity of ARDS for both FAS and PPS populations.

7.2.4 Secondary Efficacy Analysis

7.2.4.1 Mortality Analysis

Observed Mortality rates (Day 28, Overall, In ICU, In Hospital) with 95% Confidence Intervals (Clopper Pearson) will be displayed using categorical summarises (Alive/Dead) for each Treatment group (FP-1201-lyo and Placebo), Severity of ARDS (Moderate/Severe) and Overall (Tables 14.2.3.1, Figures 14.2.2).

Adjusted odds ratio estimate (including a 95% confidence interval) for the treatment effects will be displayed (in summary table (Table 14.2.3.2) and graphically (Figures 14.2.3)). Both FAS and PPS group analyses will be given for the mortality analysis.

Homogeneity of treatment effect will be assessed by calculating ORs and associated confidence intervals by ARDS severity and by country and displaying these in a Forest Plot (log scale) (Figure 14.2.3.3).

7.2.4.2 Days Free Of Mechanical Ventilation Analysis

Total number of days free of mechanical ventilation (not derived VFDsurv scores) will be numerically summarised (excluding means and standard deviations) according to Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall. Statistical significance (Van Elteren p-values) obtained will be displayed with the summaries (Table 14.2.2.1.1, Figure 14.2.4.1). Days free of mechanical ventilation will be also displayed as a frequency plot over 28 days by treatment group overall (Figure 14.2.4.2).

7.2.4.3 Days Free Of Organ Failure, Renal Support And Vasoactive Support Analysis

Totals derived will be presented as described in Section 7.2.4.2 above (Table 14.2.2.1.1, Figures 14.2.5.1 – 14.2.5.3).

7.2.4.4 Length Of ICU 'Care Free' Stay/Hospital Stay Analysis

Totals derived will be presented as described in Section 7.2.4.2 above (Table 14.2.2.1.1, Figures 14.2.6.1 – 14.2.6.2).

7.2.4.5 Sequential Organ Failure Assessment (SOFA) Analysis

Total scores and Change from baseline scores will be numerically summarised according to Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall for all patients and by country (Tables 14.2.4.1).

Contributing Cardiovascular, Respiratory, Coagulation, Hepatic, Renal and CNS organ sub scores will be similarly presented for all patients (Tables 14.2.4.2).

ANCOVA analysis of the Total SOFA score at the Last observation performed will be similarly presented (in summary Table 14.2.4.3) and graphically (Figure 14.2.7.1) with model estimates (LS means and a 95% confidence interval for the difference).

Homogeneity of treatment effect will be assessed by obtaining the difference in LS means together with 95% confidence intervals for the categories of ARDS severity using the ANCOVA model with the addition of a treatment by ARDS severity interaction term and displaying these in a Forest Plot (Figure 14.2.7.2).

7.2.4.6 Individual Organ Assessment Analysis

7.2.4.6.1 Cardiovascular Function

Vasoactive support assessments will be categorically summarised (Yes/No) with the derived Last observation performed, by Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall for each assessment time and by country (Tables 14.2.5).

7.2.4.6.2 Pulmonary Function

Ventilation assessments will be numerically summarised (with the derived Last observation performed) using the actual values and change from baseline values by Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall for each assessment time and by country (Tables 14.2.6.1 – 14.2.6.9). These include: Fraction inspired oxygen (FiO2), Partial pressure arterial oxygen (PaO2), PEEP (cm H2O), Peak inspiratory pressure (cm H2O), Plateau pressure (cm H2O), Mean airway pressure (cm H2O), Respiratory rate (bpm) and Tidal volume (mL).

ANCOVA estimates (LS means and a 95% confidence interval for the treatment difference) for the PaO_2/FiO_2 ratio change from baseline analysis will be similarly presented and by country (Table 14.2.6.10, Figure 14.2.8) for the FAS population.

Any evidence of Barotrauma will be categorically summarised (Yes/No) with the derived Last observation performed, by Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall for each assessment time and by country (Tables 14.2.6.11).

The Severity status (mild/moderate/severe/death) and Change score classifications will also be categorically summarised. The Change score CMH analysis, statistical significance (p-values) will be included (Tables 14.2.6.12).

7.2.4.6.3 Renal Function

Fluid balance monitored will be numerically summarised (with the derived Last observation performed) using the actual values and change from baseline values by Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall for each assessment time and by country (Fluid input, Tables 14.2.7.1; Fluid output, Tables 14.2.7.2; Fluid Balance, Tables 14.2.7.3).

7.2.4.7 Information from Externally Transferred Patients

Observations recorded by site staff for patients who are externally transferred between Day 7 and Day 28 will be numerically summarised (Tables 14.2.8).

7.2.4.8 Other Observations In The ICU

Other notable Procedures, Interventions, Surgeries and Diagnostics will be listed (Table 14.2.9).

7.2.5 Efficacy Evaluations - Long Term/Extended Follow Up

7.2.5.1 Patient Status Analyses

The Patient Status assessments of efficacy performed at Day 90 will be categorically summarised by Treatment group and Severity of ARDS and Overall (Tables 14.2.10.1).

Details include: Alive/Dead, Location of death (ICU/Hospital), Date of death, Location if alive (ICU/Hospital) and Requirement for assisted ventilation. All are summarised and listed.

Similarly, the patient status assessments of efficacy performed at Long Term Day 180 Follow Up and Extended Long Term Day 360 follow up will be presented in the Day 180 and Day 360 Addendum reports (Tables 14.2.10.2 and 14.2.10.3, respectively).

7.2.5.2 Quality Of Life Questionnaire Analyses

Quality of life questionnaire analyses will only be carried out at Baseline, Long Term Follow Up Day 180 and Extended Long Term Follow Up Day 360. Therefore, these results will only be presented in the Day 180 and Day 360 Addendum reports as appropriate.

The EQ-5D-3L VAS score and sub scores will be numerically summarised for actual values and change from baseline by Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall for each assessment time (Tables 14.2.11.1 and 14.2.11.3, Day 180 and Day 360, respectively).

EQ VAS score analysis will be similarly presented (in summary table and graphically) with model estimates (LS means and a 95% confidence interval for the difference in change from baseline values) (Tables 14.2.11.2 and 14.2.11.4, Figures 14.2.9.1 and 14.2.9.2, Day 180 and Day 360, respectively).

7.2.5.3 Respiratory And Neurological Function Assessment

Respiratory and Neurological function assessments are carried out at Baseline, Long Term Follow Up Day 180 and Extended Long Term Follow Up Day 360. Therefore, these results will only be presented in the Day 180 and Day 360 Addendum reports as appropriate. Table shells are displayed in Appendix 5 and 6 for Day 180 and Day 360, respectively.

7.2.5.3.1 Respiratory Function (FEV-1) Analyses

FEV-1 will be numerically summarised using actual values at Day 180 and Day 360 (Table 14.2.12.1 and 14.2.12.3, respectively). ANOVA parameter estimates (LS means and a 95% confidence interval) will be presented for each treatment group Overall and according to Severity of ARDS at each assessment time (Day 180, Table 14.2.12.2; Figure 14.2.10.1; Day 360, Table 14.2.12.4, Figure 14.2.10.2).

7.2.5.3.2 Neurological Function (6MWT) Analyses

Pre-test, During test and Post test evaluations will be summarised for each Test performed (Test One/Test Two) on Day 180 (pre-test: Tables 14.2.13.1-2, 14.2.14.1-2, 14.2.15.1-2, 14.2.16.1-2; during: Table 14.2.17.1-2; after: Table 14.2.19.1-2) and Day 360 (Tables (pre-test: Tables 14.2.13.3-4, 14.2.14.3-4, 14.2.15.3-4, 14.2.16.3-4; during: Table 14.2.17.3-4; after: Table 14.2.19.3-4)).

6MWT distances (Furthest distance walked (Test One/Two), Test One only) will be numerically summarised using actual values. ANOVA parameter estimates (LS means and 95% confidence interval) for the overall treatment difference will be presented (in summary table and graphically) for maximum distance walked and distance walked in test one on Day 180 (Tables 14.2.20.1-2, Figures 14.2.11.1-2) and Day 360 (Tables 14.2.20.3-4, Figures 14.2.11.3-4).

7.2.5.4 Study Completion / Unblinding

Long term (Day 180) and Extended follow up (Day 360) completion details will be categorically summarised according to Withdrawal (Yes/No) and the Primary Reason, and presented in the Day 180 and Day 360 Addendum reports, respectively (Tables 14.2.21.1 and 14.2.21.2). All other reasons will be listed.

A supporting Unbinding (Yes/No) categorical summary will be provided and all details listed.

7.2.5.5 Ventilation Free Survival At Day 90 Analyses

Categorical summaries including the number and percentage of patient deaths, alive but on a ventilator and breathing unassisted by Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall will be presented with CMH test statistical significance (p-values) obtained overall at Day 90 (Tables 14.2.22).

7.2.5.6 Mortality - Day 90 Report

The observed mortality is investigated using Kaplan Meier survival plots, Logrank test and Cox's PH model. A summary table showing the number and percentage of deaths/survivors, together with survival (number of days) statistics: median, lower and upper quartiles and the range will be presented overall and by country for each severity and overall by treatment (Table 14.2.23.1.1). Summaries of product limit estimators of survival and median survival times (with 95% confidence interval) and Logrank statistics will be displayed at Day 90 and include all available patient data up to Day 360 (Tables 14.2.23.2.1, Figure 14.2.12.1). Adjusted Hazard ratios (with 95% confidence interval) will also be presented (Tables 14.2.23.2.1, overall and according to Severity and Country.

Similar summaries and analyses will be carried out for the long term and extended follow-up periods at Day 180 and Day 360 including any additional available data collected since the Day 90 and Day 180 reports, respectively (Day 180: Tables 14.2.23.1.2 and 14.2.23.2.2, Figure 14.2.12.2; Day 360: Tables 14.2.23.1.3 and 14.2.23.2.3, Figure 14.2.12.3).

7.2.6 Pharmacoeconomic Analysis

Numerical summaries of overall costs and according to cost item will be presented together with ANCOVA analysis of logarithmically transformed costs. Numeric summaries will display actual values by Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall for the UK and by country if other country data become available (Tables 14.2.24.1,

Figures 14.2.13.1 and 14.2.13.2). Parameter estimates will also be presented after back transformation to obtain geometric mean estimates overall (Table 14.2.24.2).

A supplemental Incremental Cost Effectiveness Ratio (ICER) plot may also be presented for each Treatment group using the primary efficacy endpoint (VFDsurv) vs total cost of treatment for each individual patient (Figure 14.2.13.3).

As discussed, these summaries will be presented with the Day 180 and/or Day 360 long-term follow up reports to expedite the publication Day 90 statistical and clinical study reports.

7.2.7 Pharmacodynamic Endpoints Including Immunological Markers Analysis

IFN Beta-1a ADA (BAb) and NAb will be summarised categorically (using Positive/Negative classification) displaying the observed proportions with 95% Confidence Intervals (Clopper Pearson) (Tables 14.2.25.1.1 and 14.2.25.2, Figures 14.2.14) with an overall p-value (CMH). Titre values for BAb will be listed only. For the numeric biomarker variables: MxA, CD73 and other biomarkers such as PIMs, these will be summarised using the actual values and change from baseline (with the derived Last observation performed) (Tables 14.2.25.2). ANCOVA estimates (LS means and a 95% confidence interval for the treatment difference) will be presented for all numeric biomarker variables (Tables 14.2.25.3).

Both sets of summaries will be displayed by Treatment group (FP-1201-lyo/Placebo), Severity of ARDS (Moderate/Severe) and Overall by assessment.

These variables will also be displayed graphically (Figures 14.2.15 to 14.2.17).

7.3 Safety Evaluations

Specific evaluations include: Adverse events, Vital signs, Twelve lead ECG, Physical examination, and Laboratory safety tests (Biochemistry, Haematology, Urinalysis). All safety summaries will be presented according to Treatment group and Severity of ARDS (Moderate/Severe) but there will be no grouping by Country.

7.3.1 Adverse Events (AEs)

AEs will be presented according to the coded System Organ Class (SOC) and Preferred Term (PT), by Treatment group for the entire study period (Overall-irrespective of whether in ICU) and also according to when the events occurred (during Short Term Follow Up, Days 1-28 and Day 90, or during Long Term (Day 180)/Extended Follow Up (Day 360)). All AEs reported up to Day 90 will be included in the main study report. Adverse events reported between Day 90 and Day 180 will be included in the cumulative AE tables presented in the Day 180 Addendum report, which will also include all previously reported AEs. Similarly, adverse events reported between Day 180 and Day 360 will be included in cumulative AE tables presented in the Day 360 Addendum report. Additionally, any available AE data reported between long term follow up at Day 90 and long term follow up at Day 180, and long term follow up at Day 180 and extended long term follow up at Day 360 will also be included in the Day 90 main report and Day 180 long term follow up addendum reports, as described below.

The overview summary will display the number and percentage of patients, with any adverse event, PTSS and Treatment Emergent Adverse Events (TEAEs). Additionally, the table will include the number of TEAEs classed as drug-related (probably related, possibly related), TEAE intensity (mild, moderate, severe), those leading to discontinuation and TEAEs considered serious and Deaths. This table will be produced in the main report at Day 90 for: All AEs up to Day 90 (Table 14.3.1.1.1); short term follow-up, Day 1-28 (Table 14.3.1.1.2); long term follow-up, Day 28 – Day 90 (Table 14.3.1.1.3); and all available data for short and long term follow up to Day 180 (Table 14.3.1.1.4); and all available data for short, long term and extended follow up to Day 360 (Table 14.3.1.1.5). Tables 14.3.1.1.4 and 14.3.1.1.5 will be updated with any additional data and re-presented in the Day 180 and Day 360 addendum reports.

Similarly, the number and percentage of patients of each TEAE will also be summarised for each Treatment group and overall both alphabetically by SOC and PT (Tables 14.3.1.2) by period and according to event frequency (Table 14.3.1.3) as for the 'overall' tables. Tables 14.3.1.2.4 and 14.3.1.3.4 (Day 180) and Tables 14.3.1.2.5 and 14.3.1.3.5 (Day 360) will be updated with any additional data and re-presented in the Day 180 and Day 360 addendum reports. Similarly, the number (and percentage) of subjects for each PTSS will also be summarised alphabetically for each treatment group and overall (Table 14.3.1.4) in the main Day 90 report.

7.3.1.1 Treatment Emergent Adverse Events According To Relationship and Intensity

The number of patients, percentage of each TEAE event classified as Related (probably related/possibly related) to study drug will be summarised by Treatment group and overall by SOC and PT (Tables 14.3.1.5), together with the number and percentage of patients classified according to intensity (mild, moderate, severe) (Tables 14.3.1.6).

Related TEAE Table 14.3.1.5.2 (Day 180) and Table 14.3.1.5.3 (Day 360) will be updated with any additional data and re-presented in the Day 180 and Day 360 addendum reports. Similarly, AE event intensity tables for Day 180 (Tables 14.3.1.6.1.2, 14.3.1.6.2.2, 14.3.1.6.3.2) and Day 360 (Tables 14.3.1.6.1.3, 14.3.1.6.2.3, 14.3.1.6.3.3) will be presented in the Day 90 report with all available data and be re-presented and updated with any additional data in the Day 180 and Day 360 addendum reports.

7.3.1.2 Serious Treatment Emergent Adverse Events

Serious TEAEs will be presented according to the coded System Organ Class (SOC) and Preferred Term (PT), by Treatment group for the entire study period (Overall) and also according to when the events occurred (during Short Days Term Follow Up 1-28 in ICU) or during Long Term/Extended Follow Up).

Serious TEAEs will also be listed by Treatment group and patient, indicating the name of the AE, PT and SOC, together with details of the start and end dates and times, event duration (hours) and maximum intensity. Additionally, the relation to study drug, action taken, outcome and the time between the first dose of study drug and the start of the serious TEAE will also be displayed (Table 14.3.1.7.1).

The number and percentage of patients of each SAE will also be summarised for each Treatment group and overall both alphabetically by SOC and PT (Tables 14.3.1.7.2) by period and according to event frequency (Table 14.3.1.7.3) as for the 'overall' tables. Table 14.3.1.7.2.4 (Day 180) and Table 14.3.1.7.2.5 (Day 360) will be updated with any additional data and re-presented in the Day 180 and Day 360 addendum reports.

7.3.1.3 Discontinuations Due To Treatment Emergent Adverse Events

Similar tables to that for serious TEAEs will be produced for all discontinuations due to TEAEs to Day 90 (Tables 14.3.1.8.1.1 and 14.3.1.8.2.1), Day 180 (Tables 14.3.1.8.1.2 and 14.3.1.8.2.2) and Day 360 (Tables 14.3.1.8.1.3 and 14.3.1.8.2.3).

7.3.1.4 Deaths

Similar tables to that for serious TEAEs will be produced for deaths to Day 90 (Tables 14.3.1.9.1.1 and 14.3.1.9.2.1), Day 180 (Tables 14.3.1.9.1.2 and 14.3.1.9.2.2) and Day 360 (Tables 14.3.1.9.1.3 and 14.3.1.9.2.3).

A supporting categorical summary will also be presented using other collected data. These include: Time of death after randomisation (days), Location (ICU or hospital) at the Time of death (Patient Status (i.e.: partly a repeat of Patient Status data in section 6.6.1)) and Cause of death (Death Report at Day 180 or Day 360) (Table 14.3.1.10).

7.3.2 Vital Signs

Vital signs are recorded at Day 1 (Pre-dose), then at selected visits (Day 2 - 28 (In/Out Of ICU), Last day in ICU) and in the event of withdrawal, at Early Termination. The Last observation performed is also derived.

Blood pressure (systolic/diastolic), Mean arterial pressure, Heart rate, Body temperature and total respiratory rate measured will be summarised numerically for each Treatment group and Severity of ARDS (Moderate/Severe) at each assessment time (i.e.: Each Day in ICU and including Last observation performed) using the actual values and change from baseline (Tables 14.3.2).

7.3.3 Twelve Lead ECG

ECG are recorded are performed at Day 1 (Pre-dose) then on Day 7. Ventricular rate, PR, PQ Interval, QRS Duration and QTc will be summarised numerically for each Treatment group and Severity of ARDS at both assessment times (Day in ICU) using the actual values and change from baseline (Tables 14.3.3.1).

A categorical summary will be used for the overall Normal/Abnormal NCS/Abnormal CS result (Table 14.3.3.2).

7.3.4 Physical Examination

The Physical examination findings will be displayed as categorical summaries at each assessment time.

Physical examinations are performed at Screening, then at the Last day in ICU and Day 28 (Out of ICU) or Early Termination. The Last observation performed is derived. Major body systems: General appearance, Ear, nose and throat, Eyes, Respiratory, Abdomen, Urogenital, Musculoskeletal, Neurological, Lymph nodes and Skin will be categorically summarised for each Treatment group and overall and Severity of ARDS at each assessment time (Day in ICU) (Tables 14.3.4).

Predicted body weight at screening will be summarised with other demographics.

7.3.5 Laboratory Assessments

Laboratory assessments are performed at Day 1 (Pre-dose) and Day 2 - 28 (In/Out Of ICU), Last day in ICU) or at Early Termination. The Last observation performed is derived. Actual values and within patient Change from baseline (for numeric variables) for all haematology, chemistry and urinalysis will only be listed with patients identified by Treatment group, Severity of ARDS, Country and Investigational site for each assessment time using the Safety population.

Laboratory values are also classified by the Investigator as Out of range (Not clinically significant), Out of range (Clinically significant) or Out of range (Clinically significant and an Adverse event). Categorical summaries for these data will be pooled over all sites and identified according to Treatment group but not by Severity of ARDS or by Country. These summary tables will also contain Normal and Not Done (including missing) categories for comparative purposes (Tables 14.3.5.1.1, Haematology; Tables 14.3.5.2.1, Biochemistry; Urinalysis, Tables 14.3.5.3.1).

Source laboratory normal ranges for these classifications will also be presented as listings for each of the Investigational sites.

Shift tables displaying the overall change from baseline (Day 1 Pre-dose) in these categorical classifications (Out of range (Not clinically significant), Out of range (Clinically significant) or Out of range (Clinically significant and an Adverse event)) will be provided according to Treatment group for each laboratory variable relating the Last observation performed during the 28 day period in the ICU. These shift tables will also contain Normal and Not Done (including missing) categories for comparative purposes (Tables 14.3.5.4.1, Haematology; Tables 14.3.5.5.1, Biochemistry; Urinalysis, Tables 14.3.5.6.1).

Supporting listings for all the laboratory variables for each patient and each assessment time will include the actual values, clinical classification and any comments on the clinical significance of findings. Patient identifiers of Treatment group, Severity of ARDS, Country and Investigational site will be included. Additional (Unscheduled) laboratory assessments performed will only be listed.

7.4 Addendums Long Term (Day 180) & Extended Follow Up (Day 360) Efficacy And Safety Report

Data collected at Day 180 (Day 90 to Day 180) encompassing the long term follow up and Day 360 encompassing the Extended Follow Up period (Day 180 to Day 360) will be summarised separately and issued as an addendum to the Clinical Study Report (CSR). However, where appropriate any available safety data will be presented in the main report at Day 90 and/or Day 180 addendum report.

But, new table summaries will be generated and separate statistical analyses performed with the additional information available where appropriate. This applies to: Patient Status (+Mortality rate Day 180/360), Quality of life (EQ-5D-3L), Respiratory functioning (FEV-1) and Neurological functioning (6MWT).

The Overall survival rate (Time to Death) analysis will also be updated and relevant tables and figures regenerated.

Other specific table summaries relating to previously reported data will be regenerated after updating the database. This applies to: Patient Completion and Unblinding details plus all AEs and Death reports.

Table shells for the long term and extended follow up periods are given in Appendix 5 and 6, respectively.

7.5 Graphical Presentations

Key findings identified in summary and analysis tables will be presented graphically. A complete list with template shells are given in Appendix 2.

Template type 1 will present individual treatment estimates for FP-1201-lyo and placebo. Type 2 will present FP-1201-lyo - placebo differences or FP-1201-lyo / placebo ratios. Variability (95% CI) of all estimates will be indicated.

7.6 Data Listings

All data presented in summary tables will be supported by specific referenced data listings. These will identify the Patient number, Investigator site, Country id, Treatment, Visit/Day/Dose number and provide actual data and/or derived data as appropriate.

The following listings will be included in the Day 90 report only:

Listing 16.2.1.6: ICU Admission
Listing 16.2.1.8: Demographics
Listing 16.2.1.9 APACHE II Scores
Listing 16.2.1.10: Disease Diagnosis
Listing 16.2.1.11: Medical History
Listing 16.2.1.12: Prior Medications
Listing 16.2.1.16: Pregnancy Test

Listing 16.2.1.17.1: Inclusion Criteria – Part 1
Listing 16.2.1.17.2: Inclusion Criteria – Part 2
Listing 16.2.1.18.1: Exclusion Criteria - Part 1
Listing 16.2.1.18.2: Exclusion Criteria - Part 2
Listing 16.2.1.19: X-Ray Selected
Listing 16.2.1.20: Eligibility Criteria
Listing 16.2.1.21: Randomisation
Listing 16.2.1.22: Drug Administration
Listing 16.2.2.2: Externally Transferred Patients - Day 28 No Longer in ICU
Listing 16.2.2.3: Patient Status Score Derivations
Listing 16.2.2.4: SOFA
Listing 16.2.2.5: Ventilation Parameters
Listing 16.2.2.6: Fluid Balance
Listing 16.2.2.15.1: Blood Sampling for Biomarkers - IFNß BAb and NAb
Listing 16.2.2.15.2: Blood Sampling for Biomarkers – MxA
Listing 16.2.2.15.3: Blood Sampling for Biomarkers - CD73
Listing 16.2.2.15.4: Blood Sampling for Biomarkers – PIMs
Listing 16.2.3.3: Electrocardiogram (Safety Population)
Listing 16.2.3.4: Physical Examination at Screening
Listing 16.2.3.5: Physical Examination Changes

The following listings will be included in the Day 90 report **and subsequently updated** and presented again in the Day 180 and 360 addendums:

Listing 16.2.1.1.3: Patient Disposition (All Patients) - Death Reports
Listing 16.2.1.4: Deviations Day 90 Report ((All Patients))
Listing 16.2.1.5: Comments
Listing 16.2.1.7: Visit Dates
Listing 16.2.1.13: Infusion Concomitant Medications - Parts 1 – 2
Listing 16.2.1.14: Bolus Concomitant Medications - Parts 1 – 2
Listing 16.2.1.15: Vasoactive Medications
Listing 16.2.2.1.1: Patient Status - Deaths (Safety Population)
Listing 16.2.2.1.2: Patient Status - Ventilation, Renal and Vasoactive Support
Listing 16.2.2.7: Procedures, Interventions, Surgeries and Diagnostics
Listing 16.2.3.1: Adverse Events Listing (Safety Population)
Listing 16.2.3.6.1: Laboratory Values – Haemotology (for unscheduled visits only)
Listing 16.2.3.6.2: Laboratory Values – Chemistry (for unscheduled visits only)
Listing 16.2.3.6.3: Laboratory Values – Urinalysis (for unscheduled visits only)

The following listings supporting data collected only at Days 180 and 360 will be included in the addendum reports only:

Listing 16.2.1.1.1: Patient Disposition (All Patients) - Completion and Withdrawal Day 180
Listing 16.2.1.1.2: Patient Disposition (All Patients) - Completion and Withdrawal Day 360
Listing 16.2.2.8: EQ-5D-3L Assessment
Listing 16.2.2.9: FEV

Listing 16.2.2.10: Investigator's Evaluation Form for 6MWT
Listing 16.2.2.11: 6MWT Concomitant Medications
Listing 16.2.2.12: 6MWT Comorbidities
Listing 16.2.2.13.1: 6MWT Pre First Test Recordings
Listing 16.2.2.13.2: 6MWT During the First Test Recordings
Listing 16.2.2.13.3: 6MWT After the First Test Recordings
Listing 16.2.2.14.1: 6MWT Pre Second Test Recordings
Listing 16.2.2.14.2: 6MWT During the Second Test Recordings
Listing 16.2.2.14.3: 6MWT After the Second Test Recordings

Listings will be created according to the ICH guidelines, as appropriate for the data collected.

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8. References

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5-Poisson Regression
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6-Logistic regression
CYJ Penga, KL Leea & GM. Ingersolla. "An Introduction to Logistic Regression Analysis and Reporting" The Journal of Educational Research Volume 96, Issue 1, 2002

7-Kaplan-Meier / Logrank
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8-ANCOVA
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9-Cost Effectiveness Analysis
Mannings WG, Mullahy J. Estimating log models: to transform or not to transform? J Health Econ. 2001; 20:461-94.

10-Bootstrap Estimates

Cassell DL. Bootstrap Mania!: Re-Sampling the SAS® Way Paper 268 SAS Global Forum 2010

11-6MWT Guidelines
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9. Finalisation of Statistical Analysis Plan

The statistical analysis plan, and all relevant table, figures and listing 'shells' will be finalised before database lock – Day 90 CSR.

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10. Appendices to be Included in the Statistical Report

1. Summary tables
2. Figures
3. Listings supporting summary tables
4. Data derivations – contains rules for deriving efficacy variables when required
5. Long Term Follow Up Day 180 = Summary tables, figures and supporting listing (Addendum to report)
6. Extended Long Term Follow Up Day 360 = Summary tables, figures and supporting listing (Addendum to report)
