Online Resource 1: Clinical Protocol Sumary

Title:
Safety and efficacy of multipotent adult progenitor cells in acute respiratory distress syndrome (MUST-ARDS): a multicentre, randomised, double-blind, placebo-controlled phase 1/2 trial
Journal: Intensive Care Medicine

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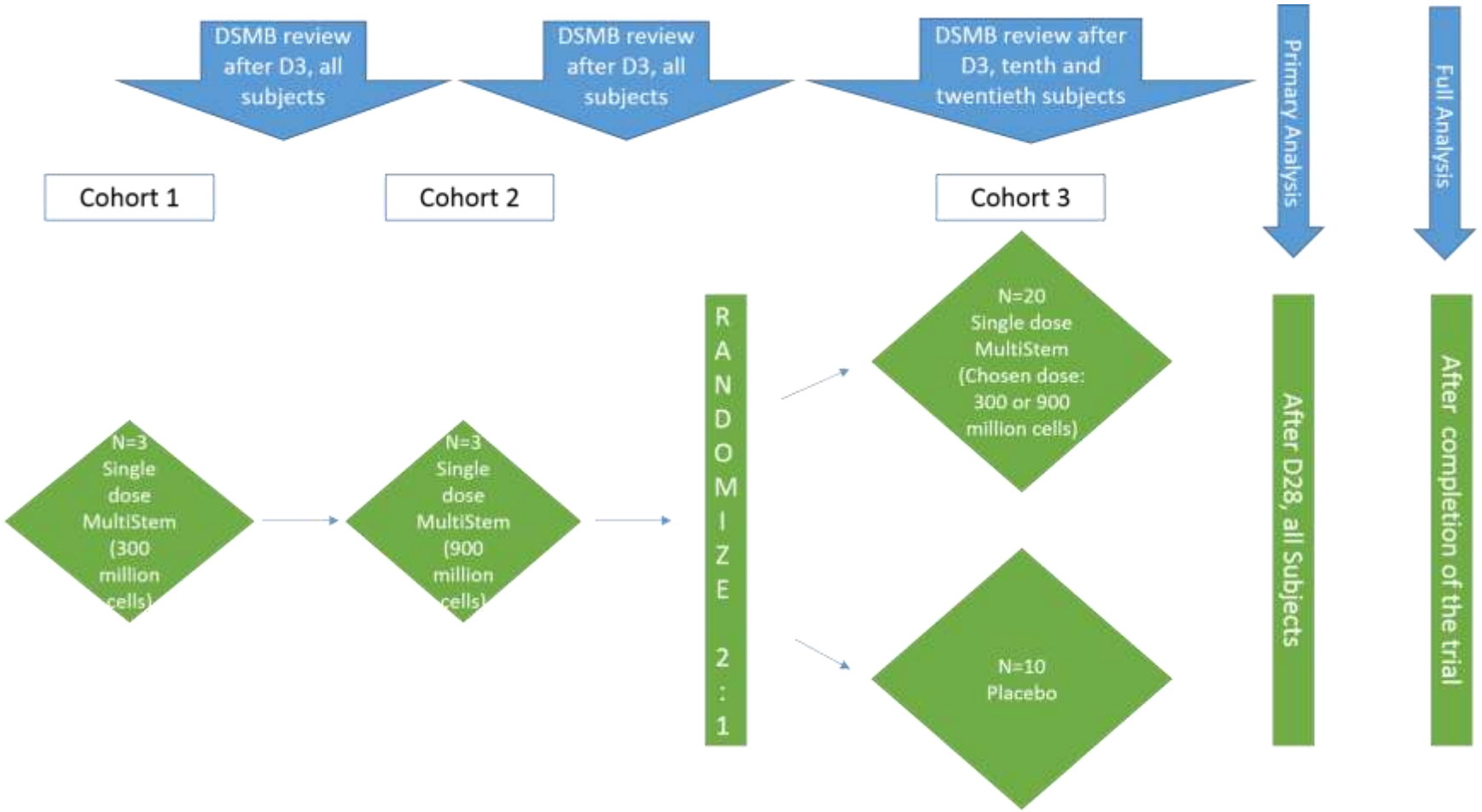
CLINICAL PROTOCOL SUMMARY

A Phase 1/2 Study to Assess the Safety and Efficacy of MultiStem® Therapy in Subjects with Acute Respiratory Distress Syndrome

Protocol Number:	B04-01
Phase:	1/2
ClinicalTrials.gov	NCT02611609
EUDRACT Number	2015-001586-96

Trial Overview



Schedule of Activities

Day	-4 to -1	0 Pre-infusion	0 Post-infusion	1[a]	2[a]	3[a]	7 [a,b]	28 [a,c] (±3 days)	90 (±7 days)	365 (±7 days)
Procedure	Screening	Baseline	Follow-up							End of Trial
Informed Consent	X									
Inclusion/Exclusion	X	X								
Demographics	X									
Physical Exam[d]	X	X				X	X	X	X	X
Medical History	X									
Height, Weight and BMI	X									
Biochemistry/Hematology	X	X		X	X	X	X			
Respiratory Function[e]	X	X[n]	X[n]	X	X	X	X	X		
Pregnancy test	X[f]									
12-Lead ECG	X									
Randomization		X								
Vital Signs	X	X[g]	X[h]	X	X	X	X			
Pre-infusion stability (2hr)[i]		X								
IMP administration			X							
Blood Sample for Exploratory Biomarkers[j]		X		X	X	X	X			
Hospitalization Data Collection								X[k]		
Quality of Life Questionnaire (QoL)								X	X[l]	X[l]
Adverse Events	X	X	X	X	X	X	X	X	X[l]	X[l]
Mortality			X	X	X	X	X	X	X[l]	X[l]
Concomitant Medications	X	X	X[O]	X	X	X	X	X[m]	X[l,m]	X[l,m]

[a] Measurements for vital signs, biochemistry, hematology, respiratory function and cytokine (biomarker) blood samples to be taken from first-readings-of-the-day.

[b] Data to be collected on the day of discharge, if discharged prior to Day 7.

[c] Outpatient clinic visit should occur if the subject is discharged from hospital prior to Day 28.

[d] Physical exam to include at least general appearance, cardiovascular, respiratory, skin, lymph nodes, abdomen.

[e] Respiratory function to include respiratory rate, tidal volume and airway pressures (peak and plateau) plus mode of ventilation and include PaO_2/FiO_2 and PEEP. Assessment to be performed only if subject is on a ventilator.

[f] Women of child bearing potential only: urine or serum pregnancy test must be negative prior to administration. If urine pregnancy is positive then a negative serum test is required.

[g] Vital signs including blood pressure, pulse, respiration, pulse oximetry and temperature will be collected 1 hour ± 30 minutes prior to infusion start.

[h] Vital signs including blood pressure, pulse, respiration, pulse oximetry and temperature will be collected every 15 ± 5 minutes for the first 2 hours and at 3 and 4 hours ± 30 minutes after infusion start.

[i] Subject is considered unstable if any of the criteria described in Section **Error! Reference source not found.** are met, although the subject can be re-evaluated for stability over additional 2-hour periods if subject is still within the 96-hour window.

[j] Exploratory blood analyses will include the measurement of total white blood cell count and absolute neutrophil count (from local laboratory sample) and inflammatory cytokine biomarkers at baseline (Day 0 Pre-Infusion) and Days 1, 2, 3 and 7.

[k] To be collected again at the time of discharge from the hospital, if subject is still hospitalized due to same incidence of ARDS at Day 28. Includes Ventilator Free Days, Hospitalization Days and ICU Days, as described in Section 0.
[l] Data to be collected by telephone call if subject is unwilling to come for an in-person visit.
[m] All concomitant medications through to and including Day 28 must be reported. Concomitant medications given to treat an adverse event with at least a possible causal relationship to the IMP, will be reported through to the End of Trial visit.
[n]: FiO2, PEEP, Inspiratory pressures – either the peak pressure or plateau pressure, mode of ventilation and PaO2 (if available) at Day 0 (dosing day), 0 hour, 1, hour, 2 hour, 3 hour and 4 hour +/- 15 mins from the start of the infusion.
[o] Changes in vasopressor and inotrope dose will be collected for 4 hours after infusion start.

TRIAL SYNOPSIS

Title: A Phase 1/2 Study to Assess the Safety and Efficacy of MultiStem® Therapy in Subjects with Acute Respiratory Distress Syndrome

Indication: Acute Respiratory Distress Syndrome (ARDS).

Objectives:

Primary Objective

The primary objective of this trial is to evaluate the acute safety and tolerability of MultiStem therapy as a treatment for subjects with ARDS.

Secondary Objective

The secondary objectives of this trial are to evaluate longer term safety, tolerability, efficacy, pulmonary function and mortality of MultiStem therapy as a treatment for subjects with ARDS.

Exploratory Objective

The exploratory objective of this trial is to evaluate biomarkers that determine the activity of MultiStem therapy as a treatment for subjects with ARDS and to assess quality of life (QoL).

Trial Product & Mode of Administration:

A single dose of MultiStem Therapy (300 or 900 million cells) will be administered by intravenous (i.v.) infusion.

Comparator Product(s) & Mode of Administration:

Cohort 3 of this study is blinded and placebo controlled. Placebo (PlasmaLyte-A, dimethyl sulfoxide, and human serum albumin) is the vehicle in which MultiStem therapy is administered, hereafter referred to as placebo. Placebo will be administered by i.v. infusion.

Number of Centers and Subjects planned:

Approximately 8 centers in the UK and USA will participate to enroll approximately 40 subjects in order to have 36 evaluable subjects.

Diagnosis and main criteria for admission to screening phase of trial:

The trial will recruit patients with ARDS, as defined by the Berlin definition, who meet eligibility criteria described below.

Inclusion criteria:

1. Male or female, age 18-90 years (inclusive);
2. Subject or legally authorized representative must freely sign informed consent after the nature of the trial and the disclosure of his/her data has been explained;

3. Diagnosis of a new acute onset of moderate to severe ARDS, as defined by the Berlin definition, requiring an endotracheal or tracheal tube with all the following criteria met, within a 24 hr period:
    a. PaO_2/FiO_2 ratio of <200 mmHg (27 kPa) on positive end-expiratory airway pressure (PEEP) of ≥5 cm H_2O;
    b. Bilateral opacities on a chest radiograph or CT scan; and
    c. Respiratory failure not fully explained by cardiac failure or fluid overload.
4. Able to receive investigational medicinal product within 96 hours of meeting the last of the ARDS diagnosis criterion defined in inclusion #3 (i.e., clock starts when last criterion is met);
5. Female subjects who are either:
    a. Not pregnant, not breastfeeding, and are not planning on becoming pregnant for 3 months from IMP administration;
    b. Not of childbearing potential, defined as one who has been postmenopausal for at least 1 year, or has been surgically sterilized, or has had a total hysterectomy at least 3 months prior to the start of this trial; or
    c. If of childbearing potential, must agree to use an effective method of contraception for 3 months from IMP administration.
6. Male subjects with female partners of childbearing potential must agree to use adequate contraceptive methods (see Section **Error! Reference source not found.**) for 3 months from IMP administration.

Exclusion criteria:

1. Moribund subject not expected to survive up to 48 hours;
2. Concurrent illness that shortens life expectancy to less than 6 months;
3. Home mechanical ventilation for chronic respiratory failure (Non-invasive ventilation (NIV) or via tracheostomy) except for Continuous Positive Airway Pressure (CPAP)/ Bilevel positive airway pressure (BiPAP) used solely for sleep-disordered breathing;
4. Diffuse alveolar hemorrhage with or without vasculitis;
5. Severe ILD needing supplemental oxygen;
6. Severe COPD with recent FEV1/FVC ratio <0.3 (if available) or the use of home oxygen;
7. History of chronic pulmonary hypertension (WHO Class III or IV);
8. History of lung transplantation;
9. ST-segment elevation myocardial infarction (STEMI) within the last 6 months;
10. Mean arterial pressure (MAP) <60 mmHg while on 2 or more vasopressors with or without cardiovascular inotropic support;
11. Severe chronic liver disease (Childs-Pugh Score >10);
12. Known anaphylaxis or religious objection to bovine or porcine products;
13. Previous autologous, allogeneic bone marrow or peripheral stem cell transplant to treat conditions other than hematologic malignancies;
14. Any history of malignancy within the last 2 years, with the exception of adequately treated basal or squamous cell carcinoma of the skin or hematologic malignancy treated with bone marrow or peripheral stem cell transplantation;
15. History of human immunodeficiency virus (HIV) infection with the most recent CD4 T lymphocyte count, measured within the prior 6 months, being less than 200 cells/mm^3 (testing of CD4 T lymphocyte count should be performed at screening for those subjects

whose series of prior counts have been considered borderline for progressive disease, those for whom a count has not been performed within the prior 6 months, or on the recommendation of the Medical Monitor after consultation with the Investigator);

16. Clinical findings that, in the opinion of the Investigator, raise significant doubt that ARDS is the primary etiology of the subject's hypoxemia and chest radiography criteria;
17. Other serious medical or psychiatric illness that, in the Investigator's opinion, would not permit the subject to be managed according to the protocol;
18. Prior participation in any other clinical trial involving administration of a novel (unapproved) investigational pharmacological agent(s) within 30 days prior to enrollment. Concurrent enrollment in observational and device trials and trials involving administration of approved pharmacological agent(s) will be considered on a case by case basis and in consultation with the Medical Monitor; and
19. Significant sustained improvement in oxygenation following initial diagnosis of ARDS (meeting inclusion #3), suggesting resolving ARDS (P/F ratio > 300 mmHg (40 kPa)). P/F ratio should be confirmed ≤300 mmHg (40 kPa) within the 6 hours prior to randomization.

Pre-infusion Stability Criteria:

In order to be eligible to receive IMP, a 2-hour stable baseline period must be achieved prior to infusion of the IMP, and the ARDS must have persisted, as confirmed by a P/F ratio ≤300 mmHg (40 kPa), measured within the 6 hours prior to randomization. A subject is considered unstable if any of the following criteria are met, although the subject can be re-evaluated for stability over additional 2-hour periods if the subject is still within the 96-hour window:

- a PEEP ≥20 cm H_2O at any point in the 2 hour pre-infusion stability period;
- a sustained change for more than 30 minutes, positive or negative, in inspired oxygen concentration of greater than 10% at any point in the 2-hour pre-infusion stability period;
- requires an increase of more than 0.1 mcg/kg/min of norepinephrine or epinephrine for blood pressure support at any point in the 2 hour pre-infusion stability period;
- requires a greater than 20% increase in dose of inotropes or vasopressors other than norepinephrine or epinephrine, which is confirmed by the Investigator to represent a clinically meaningful dose adjustment in response to cardiovascular instability;
- requires the administration of a new inotrope or vasopressor during the 2-hour pre-infusion stability period.

Methodology:

This will be a multicenter, Phase 1/2 safety and efficacy study in subjects with moderate to severe ARDS, enrolling approximately 40 subjects. The study will be conducted in 3 sequential cohorts commencing with 2 open-label cohorts allowing a single dose-escalation step followed by a randomized, double-blind, placebo-controlled cohort. The safety data from the trial will be reviewed by an independent Data Safety Monitoring Board (DSMB).

Cohort 1: 3 subjects will receive 300 million cells via i.v. infusion within 96 hours of meeting the last ARDS diagnosis criterion.

Cohort 2: 3 subjects will receive 900 million cells via i.v. infusion within 96 hours of meeting the last ARDS diagnosis criterion.

Cohort 3: This will be a double-blinded, randomized, placebo controlled cohort. There will be a 2:1 randomization to MultiStem therapy or placebo. A total of up to 20 subjects will receive MultiStem therapy (at the highest tolerated dose from Cohorts 1-2) and up to 10 will receive Placebo by i.v. infusion within 96 hours of meeting the last ARDS diagnosis criterion.

The DSMB will determine progression of the trial from Cohort 1 to Cohort 2, as well as the dose to be recommended for Cohort 3.

Subjects in Cohorts 1 and 2 will be staggered such that no 2 consecutive subjects of the first 3 subjects to be infused at each dose level will be infused within 24 hours of each other.

The population for this trial is men and women of 18-90 years of age (inclusive) with a diagnosis of moderate to severe ARDS as defined by the Berlin definition listed in the inclusion criteria. All diagnostic criteria for ARDS, as outlined in point 3 of inclusion criteria above, must have initial presentation within a 24-hour period. The 96-hour period permitted for commencing infusion of IMP starts once the last moderate to severe ARDS diagnosis criterion is met. Eligible subjects must then achieve a 2-hour stable baseline period (pre-infusion stability). Subjects achieving this are deemed suitable for infusion provided that ARDS has persisted, as confirmed by a P/F ratio $\leq$300 mmHg (40 kPa), measured within the 6 hours prior to randomization. The full 96 hours may be utilized to establish pre-infusion stability, but infusion must have commenced $\leq$96 hours from the last ARDS criterion being met. Informed consent must therefore be obtained soon after the diagnostic criteria for ARDS have been met, to allow completion of the screening procedures, eligibility assessment and pre-infusion stability, all within the 96-hour period.

In Cohorts 1 and 2, if the subject is eligible and achieves the pre-infusion stability period, then he/she will proceed to receive MultiStem therapy. In Cohort 3, once subjects are confirmed eligible and achieve the pre-infusion stability period, they may be randomized to receive either MultiStem therapy or placebo. For all subjects, Day 0 (pre-infusion) study procedures may commence on attaining pre-infusion stability.

During the combined period of establishment of pre-infusion stability, infusion itself and the 4-hour observation windows, subjects will not have their position (prone/supine) or ventilator settings changed, unless deemed medically necessary by the Investigator.

Specific study visits for data collection include Day 0 (post-infusion) and Days 1, 2, 3, 7, 28, 90, and 365. Data to be collected during the study include adverse events, physical examination, vital signs, safety laboratories, ventilator settings (PaO_2/FiO_2 ratio and PEEP requirements), respiratory physiologic measures, QoL, hospitalization data (Ventilator Free days, Intensive Care Unit (ICU) days, Hospitalization days) and exploratory biomarkers.

Endpoints:

Primary Endpoints

1. Safety and tolerability within 4 hours of MultiStem therapy administration; and
2. Suspected Unexpected Serious Adverse Reactions (SUSARs) within 24 hours of MultiStem therapy administration.

Secondary Endpoints

The secondary safety endpoints to be evaluated are Adverse Events (AEs), vital signs, laboratory parameters and mortality.

The secondary efficacy endpoints are the following:

1. Ventilator-free days from Day 0 through to Day 28,
2. ICU-free days from Day 0 through to Day 28,
3. Total length of hospital stay from Day 0 through to Day 28,
4. All-cause mortality from Day 0 through to Day 28,
5. Changes in levels of oxygenation (PaO_2/FiO_2 ratio) and PEEP requirements from baseline through Days 1, 2, 3, 7 and 28,
6. Changes in respiratory physiologic measures including lung compliance and airway resistance (peak and plateau pressures) from baseline through the time the subject is extubated; and
7. All-cause mortality at Days 90 and 365.

Exploratory Endpoints

The exploratory endpoints are the following:

1. Exploratory blood analyses will include the measurement of changes in parameters of inflammation and lung injury such as total white blood cell count, absolute neutrophil count and inflammatory biomarkers at baseline and Days 1, 2, 3 and 7; and
2. Quality of life (QoL) for subjects at Day 28, 90 and 365.

Statistical Considerations:

This is primarily a safety trial with the collection of parameters to assess if MultiStem therapy is safe and tolerated in patients with moderate to severe ARDS. This trial is not powered to detect efficacy, however, standard efficacy parameters will be assessed to evaluate potential data trends between MultiStem therapy and placebo subjects for future purposes of planning a larger trial.

Data from all cohorts may be combined for analysis of safety and efficacy data. In general, continuous data will be summarized using summary statistics and categorical data will be summarized using absolute frequencies or relative percentages.

The primary analysis will be performed once the last subject in Cohort 3 completes the Day 28 visit. This early readout will be for the purpose of future clinical trial planning with a clinical study report (CSR) generated. Key study operational team members will remain blinded to treatment assignment until completion of the trial at which point full trial analysis will be performed. Following full analysis, an addendum clinical study report will be generated.

TRIAL TREATMENTS

Trial product

Investigational medicinal product (IMP) is to be supplied by Athersys, Inc. and sent under frozen conditions (-135 degrees Celsius or below) to the cell processing facility. The cell processing facilities will store the clinical trial material under appropriate conditions.

Athersys, Inc. will supply sufficient quantities of IMP to allow for completion of the trial. The lot numbers will be recorded in the final trial report.

Records will be maintained indicating the receipt and disposition of all clinical trial product. At the conclusion of the trial, any unused IMP will be returned to Athersys, Inc. If no IMP remains, this will be indicated in the drug accountability log.

Formulation, Labeling and Packaging

MultiStem therapy will be provided in units of 300 million and 900 million cells ±20%. Other components are PlasmaLyte-A, dimethyl sulfoxide, and human serum albumin.

Labeling, packaging and release will be in accordance with the Clinical Trials Directive 2001/20/EC, GMP Directive 2003/94, Eudralex Volume 4 Annex 13 and 21 CFR Parts 210 and 211 for IMPs.

Preparation and Reconstitution

The product processing Standard Operating Procedures (SOPs), held within the study's Interactive Web Response System (IWRS), provide a detailed description of procedures on how to prepare and reconstitute MultiStem therapy.

Prior to use, the clinical trial material will be thawed and prepared for infusion by appropriate site personnel following the instructions provided and delivered for administration.

Use of Placebo

Placebo (PlasmaLyte-A, dimethyl sulfoxide, and human serum albumin) will be supplied by Athersys, Inc. and is the vehicle in which MultiStem therapy is administered. No other preparation or reconstitution is required.

Treatment Allocation

Approximately 40 subjects will be assigned to either MultiStem therapy or placebo. Subjects will be assigned to MultiStem therapy in an open-label design for Cohorts 1 and 2 (n = 3 subjects per cohort). In Cohort 3, subjects will be randomly assigned to MultiStem therapy or placebo in a 2:1 ratio, respectively. Cohort 3 will be a double-blind trial in which the subjects, Investigators, and site personnel involved in the administration and assessment of IMP will be blinded to subject treatment assignments throughout the trial. Each Cohort 3 subject who satisfies the eligibility criteria and achieves the pre-infusion stability period (see Section **Error! Reference source not found.**), will be randomized using an appropriately validated system. All IMP will be prepared and dispensed by designated unblinded site personnel at the cell processing laboratory. The IMP product label will indicate the study number, but will not indicate the treatment assignment.

The dosing schedule of the 3 treatment cohorts is summarized in Table 1, below.

Table 1 – TREATMENT DISPENSATION PER SUBJECT COHORT

Cohort	MultiStem therapy Dose[a]	Number of Subjects to Receive MultiStem therapy	Number of Subjects to Receive Placebo
1	300 million cells	3	0
2	900 million cells[b]	3	0
3	To be determined[b]	20	10

[a] Dose infused will be target cell number ±20%.
[b] Based on review of safety data from previous cohorts by the DSMB.

Administration

IMP and placebo will be administered in a volume of up to 300 mL at a delivery rate of up to 5 mL/min using a standard blood filter tubing set provided by Sponsor, by gravity i.v. infusion. Full training on administration procedures will be performed at the start of the trial and details can be found in the IWRS.

Management of Adverse Events & Complications

The Investigator may contact the Medical Monitor for advice regarding management of AEs and complications with additional information provided in the Study Reference Manual (SRM) and Appendix 0 for Definitions and Management of Infusion-Related Reactions.

Prior and Concomitant Therapy

Any medication taken by the trial subject during the trial, from point of informed consent, should be considered a concomitant medication. Concomitant medication may be given as medically indicated, without restriction. All concomitant medications through to and including Day 28 must be recorded in the subject's Case Report Form (CRF). Changes in vasopressor and inotrope dose will be collected for 4 hours after the start of infusion. Concomitant medications given to treat an

adverse event with at least a possible causal relationship to the IMP, will be recorded in the CRF through to the End of Trial visit.

At the Investigator's discretion, subjects may be administered paracetamol (acetaminophen), diphenyhydramine or equivalent anti-histamines for prophylaxis, per local policies and procedures for potential infusion related reactions. These will be recorded as concomitant medication in the CRF.

Compliance

The Investigator is responsible for maintaining specific subject records to document all investigational products dispensed, administered and returned.

Breaking the Blind

The Investigator is responsible for the medical care of subjects during the trial. In an emergency, when knowledge of the subject's treatment assignment is essential for the clinical management or welfare of the subject, the Investigator can unblind the treatment assignment. It is encouraged that the Investigator contact the Medical Monitor (or designee) before proceeding with the un-blinding process. Un-blinding should only occur for the subject in question if it is critical for treatment decision making by the Investigator for the well-being of the subject.

Prior to un-blinding the subject's treatment assignment, the Investigator should assess the relationship of an AE to IMP infusion of treatment (definitely, probably, possibly, unlikely, unrelated). If un-blinding is warranted, the Investigator must then follow the appropriate procedures to unblind an individual subject's treatment assignment.

Generally, blinding should only be broken for events that are considered to be serious, unexpected and causally related to the trial treatments, or as requested by local regulatory authorities.

If the trial blind is broken, the Investigator must detail the date and reason for un-blinding in the subject's records. The Investigator must also notify the Sponsor (and Independent Ethics Committee/Institutional Review Board (IEC/IRB) if applicable), if this has not already been done, that the trial blind has been broken. If the blind is broken due to an AE, the AE form must be completed and reported to the Sponsor (see Section 0).

Traceability Requirements

Under the EU CTD 2004/23/EC, there will be a documented trail of the IMP from donor to final product release, which will be maintained for a minimum of 30 years. The Investigator is required to maintain subject medical records as described in Section 0.

Storage, Dispensing and Return

The SOPs held within the IWRS provide a detailed description of procedures on how to store and dispense IMP.

In summary, clinical trial material will be provided to the cell processing facility frozen and should be stored as such in a locked and secured storage facility, accessible only to those individuals

authorized by the Investigator or Athersys, Inc. to process and dispense the IMP. IMP must be clearly identified from other Investigational supplies and normal hospital/practice inventory.

The Investigator is also responsible for ensuring that the investigational product has not been compromised prior to dispensing or administration. The IMP should not be repackaged or labeled prior to dispensing to the trial subject, unless otherwise detailed in the IMP Instruction Manual.

The Investigator is responsible to ensure that IMP is dispensed only to eligible trial subjects following appropriate trial procedures, as set out in the IWRS.

The Investigator or his/her appointed designee will keep accurate records of all clinical trial materials received and dispensed. At the conclusion of the trial, the clinical research associate (CRA) will account for all used and unused clinical trial material. All unused clinical trial material will be returned to the Athersys, Inc. according to instructions provided in the IWRS. The Investigator agrees not to distribute clinical trial material to any other person except those named on the FDA 1572 form and subjects participating in the trial.

Investigational Product Accountability

The Investigator is responsible to maintain accurate records of IMP shipment receipt from the Manufacturer including subject dispensing, product destruction and documentation of adequate storage of IMP while at the site.

TRIAL PROCEDURES

The trial procedures for each visit are detailed in the Schedule of Activities (see page 4) and are applicable to all cohorts.

Informed Consent

For subjects who have demonstrated the presence within a 24-hour period of all conditions of the ARDS criteria, as listed in Section **Error! Reference source not found.**, a legally-authorized representative (LAR) or equivalent will be approached by the Investigator to discuss the trial and provide informed consent, according to local policies and procedures.

Trial Screening

The 96-hour period permitted for commencing infusion of IMP starts once the last moderate to severe ARDS diagnosis criterion is met. Eligible subjects must then achieve a 2-hour stable baseline period (pre-infusion stability). Subjects achieving this are deemed suitable for infusion provided that ARDS has persisted, as confirmed by a P/F ratio ≤300 mmHg (40 kPa), measured within the 6 hours prior to randomization. The full 96 hours may be utilized to establish pre-infusion stability, but infusion must have commenced ≤96 hours from the last ARDS criterion being met. Informed consent must therefore be obtained soon after the diagnostic criteria for ARDS have been met, to allow completion of the screening procedures, eligibility assessment and

pre-infusion stability, all within the 96-hour period. This flow is described below, in Figure 1 (see page 16).

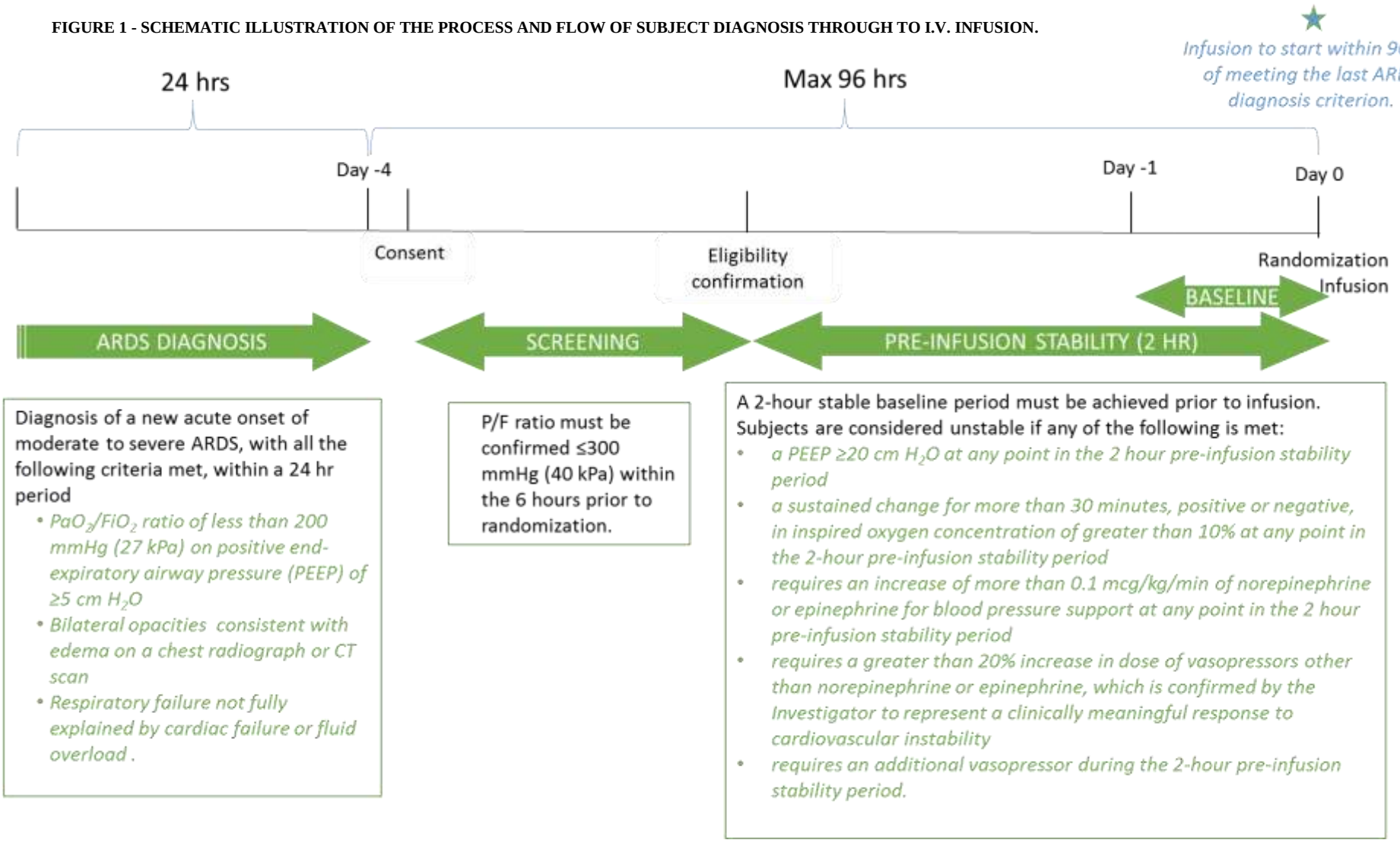
Following informed consent, each subject will undergo screening assessments to determine eligibility for the trial, as described in the Schedule of Activities and SRM.

Subject demography, medical history, adverse events and concomitant medications will be reviewed and recorded during screening visits. Clinical blood safety tests will be collected and assessed as detailed in Section 0 and the laboratory manual.

The Investigator will document review of eligibility criteria including relevant laboratory results to confirm subject eligibility.

In Cohorts 1 and 2, if the subject is eligible and achieves the pre-infusion stability period, then he/she will proceed to receive MultiStem therapy. In Cohort 3, once subjects are confirmed eligible, and achieve the pre-infusion stability period, they may be randomized to receive either MultiStem therapy or placebo.

FIGURE 1 - SCHEMATIC ILLUSTRATION OF THE PROCESS AND FLOW OF SUBJECT DIAGNOSIS THROUGH TO I.V. INFUSION.



Trial Baseline and Administration

Subjects in Cohorts 1 and 2 will be staggered such that no 2 consecutive subjects of the first 3 subjects to be infused at each dose level will be infused within 24 hours of each other.

In order to be eligible to receive IMP, a 2-hour stable baseline period must be achieved prior to infusion of the IMP and the ARDS must have persisted, as confirmed by a P/F ratio ≤300 mmHg (40 kPa), measured within the 6 hours prior to randomization. The subject can be re-evaluated for stability over additional 2-hour periods if the subject is still within the 96-hour window:

- a PEEP ≥20 cm H_2O at any point in the 2 hour pre-infusion stability period;
- a sustained change for more than 30 minutes, positive or negative, in inspired oxygen concentration of 10% at any point in the 2 hour pre-infusion stability period;
- requires an increase of more than 0.1 mcg/kg/min of norepinephrine or epinephrine for blood pressure support at any point in the 2 hour pre-infusion stability period requires a greater than 20% increase in dose of inotropes or vasopressors other than norepinephrine or epinephrine, which is confirmed by the Investigator to represent a clinically meaningful dose adjustment in response to cardiovascular instability; and
- requires the administration of a new inotrope or vasopressor during the 2-hour pre-infusion stability period.

If during the 2-hour pre-infusion stability period the subject becomes unstable, there is the option to restart the 2-hour pre-infusion stability period. The stability baseline can be repeated as many times as needed for the subject to achieve stability, provided that the subject is still within window to allow dosing to initiate within the 96-hour window. Assessments as described in the Schedule of Activities will be performed to provide a baseline for the subject.

Note that during the combined period of establishment of pre-infusion stability, infusion itself and the 4-hour observation period referenced below, subjects will not have their position (prone/supine) or ventilator settings changed, unless deemed medically necessary by the Investigator.

Following completion of baseline assessments, IMP should be administered according to Section 0 and as detailed in the IWRS. At the Investigator's discretion, subjects may be administered prophylactic paracetamol (acetaminophen), diphenyhydramine or equivalent anti-histamines per local policies and procedures according to Section 0. The infusion must start no later than 96 hours after the last criterion for diagnosis of ARDS has been met.

Follow Up

Subjects will be monitored post-administration for infusion-related reactions. Vital signs including blood pressure, pulse, respiration, pulse oximetry and temperature will be collected every 15 minutes for the first 2 hours and at 3 and 4 hours after infusion start as described in the Schedule of Activities. Specific study visits for data collection include Day 0 (post-infusion) and Days 1, 2, 3, 7, 28, 90, and 365. Data to be collected during the study will include AEs, physical examination, vital signs, safety laboratories, respiratory function, QoL, hospitalization data and exploratory biomarkers as detailed in the Schedule of Activities. Visits to Day 7 are intended to take place

whilst the subject is still in hospital. If the subject is discharged prior to Day 7 then the Day 7 data collection will be performed on the day of discharge. Longer term follow-up will take place to Day 365 post infusion as described in the Schedule of Activities. The Investigator should document all efforts to get a subject to return to complete trial procedures. The subject will be deemed as Lost-to-Follow up once the Investigator has completed minimum 3 phone calls followed by a certified letter to the last known address of the subject or next of kin, as appropriate, with no response obtained.

End of Trial

The end of the trial will have been reached when the last remaining enrolled and infused subject for the trial has completed the Day 365 visit or otherwise terminates (withdraws, is withdrawn or dies) before the End of Trial visit.

Subject Withdrawal

Subjects may withdraw from the trial at any time at their own request. The Investigator or Sponsor may withdraw a subject for safety, behavioral, or administrative reasons. Any subject may be withdrawn from the trial at the discretion of the Investigator should he/she feel it is in the best interests of the subject.

For any subject who prematurely discontinues from the trial, the reason and date of discontinuation will be documented in the CRF. The Investigator is responsible to ensure all safety assessments and final follow up assessments, including follow up for unresolved AEs, are completed prior to subject discontinuation (see below). If the subject does not return for a scheduled visit, the Investigator must make every effort (documented phone calls and registered letter) to contact the subject.

The Investigator is required to follow-up the subject for long-term data even after the subject has decided to withdraw from the trial, as long as they consent for this data to be collected or as required by the relevant Competent Authority or Ethical Committee.

If a subject requests withdrawal from the trial and also withdraws consent to allow any further information to be collected, no further trial evaluations should be conducted and no further trial data should be collected. The Investigator is responsible to ensure to his best ability, subject safety and well-being. The Sponsor reserves the right to continue to use the data collected prior to withdrawal of consent.

The trial or part of the trial may be suspended or terminated at any time by the Sponsor, Investigator, IEC/IRB or Regulatory Authorities. If the Sponsor suspends or terminates the trial or part of the trial, the Investigators, IEC/IRB and Regulatory Authorities will be promptly notified in writing with the reason for suspension/termination as per applicable regulatory requirements.

Subject Replacement

Subjects who are consented but do not meet eligibility criteria will be considered screen failures. Subjects who are enrolled or randomized but who do not receive IMP, may be replaced.

TRIAL ASSESSMENTS

Clinical Efficacy Assessments

Respiratory Function

The levels of oxygenation (PaO_2/FiO_2 ratio) and PEEP requirements will be measured at baseline through Days 1, 2, 3, 7 and 28.

Changes in respiratory physiologic parameters including lung compliance and airway resistance (peak and plateau pressures) will be measured from baseline through the time the subject is extubated. FiO2, PEEP, Inspiratory pressures – either the peak pressure or plateau pressure, mode of ventilation and PaO2 (if available) will be collected at Day 0 (dosing day), 0-hour, 1-hour, 2-hour, 3-hour and 4-hour.

Ventilator Free Days

The Ventilator Free Days assessment is a count of the number of days the subject is off the ventilator from Day 0 through to Day 28. The number of days on ventilator will be counted and then used to calculate the Ventilator Free Days. Days that subjects are weaning off and on the ventilator will be counted as partial days. Partial days will be captured in 12-hour increments rounded up to the nearest whole day. If subject is still hospitalized due to same incidence of ARDS at Day 28, data will be collected again on day of discharge.

Hospitalization Days

The Number of Days in Hospital assessment is a count of the number of total days subject remains hospitalized, from Day 0 through to Day 28. Days will be counted in 24-hour periods, partial days will be rounded to the nearest whole day. If subject is still hospitalized due to same incidence of ARDS at Day 28, data will be collected again on day of discharge.

Intensive Care Unit (ICU) Days

The Number of Days in ICU assessment is a count of the number of days subject was in the ICU from Day 0 through to Day 28. Days will be counted in 24 hour periods, partial days will be rounded to the nearest whole day. If subject is still hospitalized due to same incidence of ARDS at Day 28, data will be collected again on day of discharge.

Quality of Life Questionnaire (EQ-5D)

The Quality of Life tool that will be utilized in this study is the EQ-5D questionnaire. This is a self-administered health state questionnaire [APPENDIX 4] that will be obtained at Days 28, 90 and 365.

Clinical Safety Assessments

Safety Laboratory (Local Laboratory)

Before the start of the trial, the Investigator will provide to the Sponsor a list of normal reference ranges and units for measurement for all assessments to be conducted, and current laboratory certification. The Investigator must provide updated reference ranges and certification throughout the duration of the trial, as applicable.

All standard blood tests will be performed at the site by a certified clinical laboratory. Laboratory certification (including expiration date) and normal reference ranges for all laboratories used during the trial will be on file prior to trial initiation. Blood samples will be collected and processed per the institutional requirements and local processes.

Following IMP infusion, the Investigator will need to review laboratory values for those outside of normal range and will be required to conduct clinically appropriate follow-up procedures. Clinical significance of the values outside of normal ranges will be assessed by the Investigator.

The following analytes will be measured according to timing specified in the Schedule of Activities:

- Biochemistry: Alkaline phosphatase, ALT and/or AST, total bilirubin, blood urea nitrogen or blood urea (as appropriate), creatinine, sodium, potassium, chloride, bicarbonate, glucose, and calcium; and
- Hematology: Hemoglobin, hematocrit, red blood cell count, white blood cell count and differential and platelets.

Vital Signs

Blood pressure, pulse, respiration, pulse oximetry, and temperature will be measured. For individual time points for measurement, see Schedule of Activities.

Blood pressure, pulse, respiration, and pulse oximetry will be measured in the same position throughout intubation. Upon discharge the position may change but must be continued for the remaining study visits.

Physical Examination

The following body systems will be examined: general appearance; skin; lymph nodes; respiratory; cardiovascular; and abdomen. The Investigator should record any abnormal findings as part of the medical records and CRFs.

The Investigator should determine if changes or new findings upon physical examination, particularly if considered significant should be reported as an AE. Expected progression, signs, or symptoms of underlying disease do not need to be reported as an AE, unless more severe than expected for the subject's condition.

Electrocardiogram (ECG)

A 12-lead ECG will be conducted at screening and otherwise, as clinically indicated. The Investigator will evaluate ECGs for abnormal results and document clinical significance of these, reporting as AEs where appropriate.

Exploratory Assessments (Central Laboratory)

A blood sample for exploratory blood marker evaluation (cytokine markers) will be drawn according to Schedule of Activities. For blood sampling procedures, including information on blood volume, collection tubes, sample processing, storage, and shipping, see the Laboratory Manual for this trial. Samples will be sent to a central laboratory for analysis.

Changes in parameters of inflammation and lung injury will be measured. These blood measurements include total white blood count and absolute neutrophil count (from local laboratory sample) and inflammatory biomarkers at baseline (Day 0 Pre-infusion) and Days 1, 2, 3 and 7.

ADVERSE EVENT REPORTING

The Investigator (or site staff) will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the Investigator must seek and obtain information sufficient to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE. The Investigator is required to assess causality.

For all AEs with a causal, or suspected causal relationship to the investigational product, follow-up by the Investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and Sponsor agrees with that assessment.

Definition of an AE

An AE is any symptom, sign, illness or experience in a clinical trial subject who is administered a product or device, which develops or worsens in severity during the course of the trial. The event may not necessarily be causally related to the treatment or administration.

Worsening of disease under study is not considered an AE unless it is associated with a SAE.

Abnormal clinical findings, except those expected to be observed with ARDS events as described in Section 0, are considered to be an AE if the abnormality:

- Is associated with a change in subject dosing outside of the protocol stipulated dose adjustments or results in trial withdrawal;
- Is associated with a SAE;
- Is associated with clinical signs or symptoms;
- Requires additional diagnostic testing, or medical/surgical intervention; and
- Is considered by the Investigator or Sponsor to be of clinical significance.

Definition of AEs of Special Interest for MultiStem therapy

The following are adverse events of special interest:

- Any subject experiencing any adverse event of special interest assessed through 4 hours post-infusion that is related to investigational medicinal product:
    - Sustained hypoxemia, of more than 30 minutes, related to the infusion of the investigational product requiring an increase in the fraction of inspired oxygen of ≥0.2 and increase in PEEP level of 5cm H_2O or more to maintain transcutaneous oxygen saturations in the target range of 88-95%; and
    - Sustained hypotension, of more than 30 minutes, related to the infusion of the investigational product requiring an increase in vasopressor or inotrope dose, or addition of a new vasopressor or inotrope which is confirmed by the Investigator to represent a clinically meaningful dose adjustment/addition of vasopressor or inotrope in response to cardiovascular instability.
- Any subject experiencing any adverse event of special interest assessed through 3 days post-infusion that is related to investigational medicinal product:
    - New cardiac arrhythmia related to the infusion of the investigational product requiring cardioversion; and
    - New ventricular tachycardia, ventricular fibrillation or asystole related to the infusion of the investigational product.

NOTE: Investigator or designee should report any of these events to the Medical Monitor within 24 hours of becoming aware of the event or immediately if event is life threatening or fatal.

Definition of a SAE

A SAE, serious adverse reaction (SAR) or unexpected serious adverse reaction means any AE, adverse reaction or unexpected adverse reaction respectively that:

- results in death;
- is life threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect; and
- is an important medical event.

Important medical events are those which require intervention to prevent one or more of the other criteria listed above.

Any initial admission (even if less than 24 hours) to a healthcare facility meets the criteria of hospitalization. This does not include hospitalization for a pre-existing condition, not associated with incidence of a new adverse event or worsening of the pre-existing condition. This also does not include hospitalizations due to social or administrative reasons, or for pre-planned admissions such as protocol-defined hospital stay or for pre-planned treatments, procedures or optional admission not associated with an AE.

Hospitalization or prolongation of hospitalization also includes transfer within the hospital to an acute/ICU. Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself a SAE. Hospitalization does not include rehabilitation facilities, hospice facilities, skilled nursing facilities, routine emergency room admissions or same-day surgeries (outpatient/ambulatory care).

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE.

Any AE that does not meet the criteria for a SAE should be considered as a non-serious AE.

Severity Assessment

For infusion-related reaction events, the Investigator will rate the severity (intensity) of each event according to the CTCAE v4.0 as described below:

- Mild (CTCAE v4.0 Grade 1): Mild transient reaction; infusion interruption not indicated; intervention not indicated;
- Moderate (CTCAE v4.0 Grade 2): Therapy or infusion interruption indicated, but responds promptly to symptomatic treatment (e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours;
- Severe (CTCAE v4.0 Grade 3): Characterized as prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae;
- Life-threatening (CTCAE v4.0 Grade 4): Characterized as life-threatening consequences; urgent intervention indicated; or
- Death (CTCAE v4.0 Grade 5): death-related AE.

For all other AEs, the following guidelines will be used to assess severity:

- Mild - awareness of sign, by subject and/or physician, or awareness of symptom by subject but easily tolerated, with no impact on the management of the subject by clinical team and/or interference with subject's usual activity.
- Moderate – of a nature to require amendment/addition to clinical management plan and/or enough discomfort to subject to cause some interference with usual activity.

- Severe – of a nature to require significant amendments/additions to clinical management plan and/or urgent medical attention and/or incapacitating with inability to work or significant interference with usual activity.

A severe AE is not reportable as a SAE unless it meets the criteria as described in Section 0.

Causality Assessment

The Investigator must provide assessment of causality for all AEs (serious and non-serious). The relationship of an AE to the infusion of IMP is to be assessed according to the following definitions:

- Definitely related: Follows a reasonable temporal sequence from IMP administration; abates upon discontinuation of the IMP (dechallenge); and is confirmed by reappearance of the reaction on repeat exposure to the IMP (rechallenge) (i.e. reinitiation of IMP infusion after brief interruption);

  NOTE: dechallenge or rechallenge is not mandatory and the Investigator can use discretion as to whether a dechallenge or rechallenge would be appropriate and/or safe for the subject.

- Probably related: Follows a reasonable temporal sequence from IMP administration; abates upon discontinuation of the IMP (dechallenge); and cannot be reasonably explained by the known characteristics of the subject's clinical state; (dechallenge can be performed at the Investigator's discretion);

- Possibly related: Follows a reasonable temporal sequence from IMP administration and could have been produced by the subject's state or by other modes of therapy administered to the subject;

- Unlikely related: The temporal sequence between the AE and the IMP administration is such that the drug is not likely to have had any reasonable association with the observed event and the AE could have been produced by the subject's clinical condition or by other modes of therapy administered to the subject; or

- Unrelated: The AE is definitely produced by the subject's clinical condition or by other modes of therapy administered to the subject and the AE does not follow a temporal sequence from IMP administration.

- In the case of a report of 'Unknown' for an AE (serious or non-serious), the Investigator is required to further investigate the event to the best of his ability to provide an updated causality assessment. If the Investigator's causality assessment is 'Unknown' then the event will be handled as 'Related to investigational product' for reporting purposes.

If the event is 'Unrelated' or 'Unlikely related' to the test drug, the Investigator must document the most likely cause of the AE.

Expectedness

The Sponsor, who may request input from the DSMB, will undertake an evaluation of expectedness based on information provided by the Investigator for the adverse reaction and the single safety reference document will be the most current IB (and safety updates/amendments) for MultiStem therapy.

Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAE and expedited reporting is required, per local and international regulations.

The Sponsor will report emerging safety data as required by relevant Regulatory and Ethics Committee reporting requirements including, but not limited to: Expedited Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs), Annual Safety Reports and quarterly safety reports.

All AEs, except those expected ARDS events described in Section 0, through and including Day 365 visit are to be reported in the CRF, using precise medical terminology.

Expected ARDS Events not qualified as AEs/SAEs

Any AEs or SAEs considered to be unrelated or unlikely related to IMP (see Section 8.3), and in the opinion of the Investigator represent clinical signs of ARDS or its etiology(ies), are not reportable to Regulatory Authorities under this protocol.

Expected events for ARDS are untoward clinical occurrences that are perceived by the Investigator to occur with reasonable frequency in the day to day care of patients with ARDS treated in an ICU with mechanical ventilation. Examples of events that are expected in the course of ARDS include transient hypoxemia, agitation, delirium, nosocomial infections, skin breakdown, and gastrointestinal bleeding. Such events, which are often the focus of prevention efforts as part of usual ICU care, will not be considered reportable adverse events unless the event is considered by the Investigator to be associated with the study cell product or study procedures, or unexpectedly severe or frequent or a change of severity for an individual patient with ARDS.

Serious Adverse Events

The Investigator must report any SAEs (see Section 0) or Exposure in-utero (see section 0) within 24 hours of becoming aware of the event. In the case of fatal or life-threatening events, the Investigator should endeavor to report the event immediately. If there is a delay between the occurrence of a SAE and the Investigator becoming aware of it, the Investigator must report the event within 24 hours of learning of the event and document the time at which he/she becomes aware of it. This timeframe also applies to (new) follow-up information of an already reported SAE.

The Sponsor may request additional information regarding the SAE than originally requested on the SAE form. The Investigator is responsible to provide this additional information. In the case of a fatal SAE, the autopsy report or summary of autopsy findings must be sent to the Sponsor.

The Investigator will provide notification of SAEs to the Sponsor's Pharmacovigilance representative named in the trial contact list of the SRM. In addition, the Sponsor and the

Independent Ethics Committee/Institutional Review Board will also be informed according to their requirements.

SAEs are also to be reported on the CRF and submitted to the Sponsor. The Investigator should ensure that information captured both on the CRF and SAE Form is consistent.

Exposure in-utero

Exposure in-utero is defined as a female who becomes pregnant, or is found to be pregnant while being directly exposed to an investigational product, or if the female becomes, or is found to be pregnant having been previously exposed to an investigational product and since discontinued.

If any trial subject or a subject's partner becomes pregnant, or is found to be pregnant while receiving investigational product, the Investigator must report the pregnancy within 24 hours of awareness to the Sponsor, including the anticipated date of delivery.

The Investigator must follow the pregnancy until completion or until termination, and notify the Sponsor of the outcome. A SAE Form must be submitted, within 24 hours of awareness to the Sponsor, if any of the following occur, irrespective of causality:

- spontaneous abortion, including miscarriage and missed abortion;
- stillbirth;
- neonatal death that occurs within 1 month of birth; or
- congenital anomaly, including that in an aborted fetus, stillbirth or neonatal death.

In addition, any neonatal death that occurs after 1 month of birth and Investigator assesses that it is related to the exposure in-utero must be reported as a SAE.

Reporting Period

Non-SAEs (AEs) should be reported in the CRF through to Day 365 visit.

SAEs require immediate notification to Sponsor or its designated representative beginning from initiation of IMP administration through to the Day 365 visit.

Eliciting Adverse Event Information

At each contact with the subject, the Investigator is responsible to seek information on adverse events by specific questioning and as appropriate, examination. The Investigator must report all AEs, whether they are observed, or volunteered by the subject.

DATA ANALYSIS/STATISTICAL METHODS

A Statistical Analysis Plan (SAP) will be prepared to provide additional details on the approach to analyses and data displays. The SAP will be finalized before the database is locked for the primary analysis described below.

Sample Size Determination

This is primarily a safety trial with the collection of parameters to assess if MultiStem therapy is safe and tolerated in ARDS subjects. This trial is not powered to detect efficacy, however, standard efficacy parameters will be assessed to evaluate potential data trends between MultiStem therapy and placebo subjects for future purposes of planning larger trials.

Analysis Populations

All criteria used to define analysis populations, including Intent to Treat (ITT) and Per Protocol (PP) populations, will be identified and defined, in the SAP prior to database lock for the primary analysis.

Intent to Treat (ITT) Population

The ITT population will be defined as subjects who have achieved the 2-hour stability period, have been randomized, and have received an IMP infusion.

Per Protocol Population (PP)

The PP population will be defined as subjects who have achieved the 2-hour stability period, have been randomized, have received an IMP infusion, and have not had any major protocol deviations or violations which would impact the integrity of the data.

Statistical Considerations

Data from all cohorts may be combined for analysis of safety and efficacy data. In general, continuous data will be summarized using summary statistics and categorical data will be summarized using absolute frequencies or relative percentages.

Primary Analysis

The primary analysis for safety and efficacy will be performed once the last subject in Cohort 3 completes the Day 28 visit. The database will be locked for evaluability review and un-blinding of the data prior to analysis. This early readout will be for the purpose of future clinical trial planning with a clinical study report (CSR) generated. Key study operational team members will remain blinded to treatment assignment until completion of the trial at which point full trial analysis will be performed with an addendum CSR generated.

AEs will be classified according to the MedDRA dictionary and will be presented by counting the number of subjects reporting each event by treatment. The number and percentage of subjects reporting AEs will be tabulated by system organ class and preferred term. AEs will also be summarized by both severity and relationship to study drug. SAEs and AEs leading to withdrawal will also be summarized.

Secondary Analysis

The secondary safety endpoints to be evaluated are: AEs, vital signs, laboratory parameters and mortality.

Summaries by time point will be produced for mortality vital signs, ECG results, hematology, and biochemistry, together with changes from baseline (except mortality).

The incidence of laboratory test results outside the normal range will be summarized descriptively. Laboratory test results outside the normal range will be individually listed for clinical review.

Exploratory Analysis

Exploratory blood analyses will include the measurement of changes in parameters of inflammation and lung injury such as total white blood cell count, absolute neutrophil count and inflammatory biomarkers at baseline and Days 1, 2, 3 and 7.

Quality of life (QoL) for subjects, Day 28, 90 and 365.

DATA SAFETY MONITORING BOARD (DSMB)

An independent Data Safety Monitoring Board (DSMB) with multidisciplinary representation will be established to evaluate accumulating trial data and to assess the ongoing safety of the trial for the subjects enrolled. Assessments will be performed 3 days post-infusion of the last subject in Cohorts 1 and 2. The DSMB will determine progression of the trial from Cohort 1 to Cohort 2, as well as the dose to be recommended for Cohort 3. In Cohort 3, assessment will be performed 3 days post-infusion of approximately the 10^{th} and 20^{th} subjects enrolled. Following each data review, the DSMB will make a recommendation to the Sponsor regarding continuation, revision of dosage, or termination of the trial. Where the DSMB recommends that modification of the protocol is required and the Sponsor is in agreement, the protocol will be amended and submitted to Regulatory Authorities and Ethics Committees/Institutional Review Board for approval. Details related to the DSMB responsibilities, authorities, and procedures will be documented in the Independent DSMB charter, which will be finalized by the DSMB prior to the first subject dosed.

Enrollment Stopping Rules

In the event that any of the following is encountered, the DSMB will convene to determine if the trial must stop enrollment and/or to recommend modification to the protocol:

- Any subject experiencing any adverse event of special interest assessed through 4 hours post-infusion that is related to investigational medicinal product:
    - Sustained hypoxemia, of more than 30 minutes, related to the infusion of the investigational product requiring an increase in the fraction of inspired oxygen of $\geq$0.2 and increase in PEEP level of 5cm H_2O or more to maintain transcutaneous oxygen saturations in the target range of 88-95%; and
    - Sustained hypotension, of more than 30 minutes, related to the infusion of the investigational product requiring an increase in vasopressor or inotrope dose, or addition of a new vasopressor or inotrope which is confirmed by the Investigator to

represent a clinically meaningful dose adjustment/addition of vasopressor or inotrope in response to cardiovascular instability.

- Any subject experiencing any adverse event of special interest assessed through 3 days post-infusion that is related to investigational medicinal product:
    - New cardiac arrhythmia related to the infusion of the investigational product requiring cardioversion; and
    - New ventricular tachycardia, ventricular fibrillation or asystole related to the infusion of the investigational product.
- Any subject experiencing greater than or equal to Grade 3 infusion related reaction (CTCAE v4.0) in the first 24 hours post-infusion (see Table 2 below and Appendix 0 for Definitions and Management of Infusion-Related Reactions)

Table 2 - CTCAE v4.0 Grade of Infusion-Related Reactions*

CTCAE Grade	Description
1	Mild transient reaction; infusion interruption not indicated; intervention not indicated
2	Therapy for infusion interruption indicated but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDS, narcotics, i.v. fluids), prophylactic medications indicated ≤24 hours
3	Prolonged (e.g. not rapidly responsive to medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae
4	Life-threatening consequences; urgent intervention indicated
5	Death

* Definition: a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.

Where the DSMB recommends suspension of the trial and the Sponsor is in agreement, an internal safety review will be held to determine whether the trial can be re-started. If it is agreed that the trial should be re-started, safety data and recommendations from the internal safety review together with a protocol amendment (if appropriate) will be submitted to Regulatory Authorities and Ethics Committees for approval prior to re-start.

QUALITY CONTROL AND QUALITY ASSURANCE

Monitoring, Auditing and Inspecting

The Sponsor will be responsible for selecting Investigators qualified by education, training and experience. Curriculum Vitae and signed 1572 will be submitted to Regulatory Authorities as required.

The Sponsor is also responsible for the monitoring of the Investigator sites to ensure that the trial is being conducted per GCP and applicable regulations, including compliance to the protocol, accuracy of data reported, drug accountability and document retention (Investigator Site File). The Investigator must allow the Sponsor and its representative's direct access to all source documents (e.g. medical records, study charts, subject notes etc.) and trial documents for this verification process. The Investigator and relevant personnel must be present for monitoring visits, wherever possible, and allow sufficient dedicated time to facilitate the visit.

Monitoring visits and general, day-to-day site management will be performed by a clinical research associate (CRA), who will be responsible for ensuring that activities on site are conducted according to ICH GCP. The CRA will monitor IMP administration records under blinded conditions.

Another CRA who is unblinded to treatment assignment will monitor un-blinded accountability records of dose preparation.

The Investigator site may be subject to review by the IEC/IRB or to quality assurance audits performed by the Sponsor and its representatives, or to inspection by national or foreign regulatory authorities.

Protocol Modification

Any changes to the protocol that may impact the conduct of the trial, or affect subject safety, requires a formal amendment to the protocol. Such amendments will be agreed/approved by the Sponsor, the Investigator, Regulatory Authorities and IEC/IRB prior to implementation.

If a change is necessary to eliminate an immediate hazard to the trial subjects, it may be implemented prior to IEC/IRB approval. The Investigator should attempt to contact the Sponsor prior to implementation, wherever possible. In any case, the Investigator is responsible for notifying the Sponsor and IEC/IRB in writing within 5 working days after implementation of the change.

Protocol Deviations

Any deviations from the protocol will be recorded and reviewed routinely during the trial period through monitoring activities. Training will be provided to an individual site or all sites upon identification of non-compliance with the protocol. The Investigator will submit a list of protocol deviations according to IEC/IRB requirements. The Sponsor will routinely monitor and assess deviations to identify if any serious breach of GCP has been incurred and will ultimately reconcile the list of protocol deviations to be included in the CSR.

DATA HANDLING AND RECORD KEEPING

Case Report Form

A CRF in electronic format (eCRF) is required to be completed at site and retained for each trial subject participating in the trial and is verifiable by the CRA as per the Monitoring Plan. The Investigator is responsible to ensure accurate completion of the eCRF, and for its review and approval. The Investigator holds personal responsibility for the accuracy and authenticity of all clinical and laboratory data contained within the eCRF. By signing the eCRF, the Investigator or authorized personnel, is attesting that the data contained within the eCRF is accurate and true.

Source data are considered to be information contained in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data is contained in source documents. All information entered in the eCRF must be reflected in source documents.

The eCRF is the property of the Sponsor and must not be disclosed in any form to third parties, except for authorized representatives of the Sponsor or regulatory authorities, without prior written permission of the Sponsor.

Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements. All trial site personnel will be provided secure access and required to log into the system using their secure user name and password to enter, review, or correct trial data. These procedures will comply with the Title 21 Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

Data Validation

Validation checks programmed within the Electronic Data Capture (EDC) system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

Electronic CRFs must be reviewed and electronically signed by the Investigator.

Record Retention

The Investigator is responsible for retaining adequate information regarding the subject's identity so that regulatory authorities or the Sponsor may access the information, if necessary.

The Investigator agrees to retain all relevant trial documents (e.g., including signed subject informed consent forms, source documents, copies of CRFs, IEC/IRB approvals, investigational product records, etc.) to enable review and/or audits by Sponsor and/or regulatory authorities. These records should be retained for a period of 30 years after the end of Trial Notification to the

local Ethics Committee and Competent Authorities as described in the Clinical Trial Agreement (CTA).

If the Investigator withdraws from the trial, for any reason, records may be transferred to a suitable designee or to the Sponsor. The Investigator must notify the Sponsor in writing of withdrawing from the trial and agree upon transfer of records prior to departure.

ETHICS

Institutional Review Board (IRB)/Independent Ethical Committee (IEC)

The Investigator is responsible to have approval of the protocol, protocol amendments, informed consent forms and any relevant study documents by a properly constituted IEC or IRB prior to commencement of the trial. All correspondence, including the approval, will be filed in the Investigator Site file and copies of all approvals will be provided to the Sponsor. The Investigator is responsible for providing any significant information regarding the trial conduct or trial drug to the IEC/IRB.

Ethical Conduct of the Trial

The trial will be performed in accordance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines, and applicable local regulatory requirements and laws.

Subject Information and Consent

The informed consent form must be agreed to by the Sponsor and the IRB/IEC and must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each trial subject (or their legally authorized representative) is fully informed about the nature and objectives of the trial and possible risks associated with participation. The Investigator will obtain written informed consent from each subject (or their legally authorized representative). before any trial-specific activity is performed. The informed consent form used in this trial, and any changes made during the course of the trial, must be approved by both the IRB/IEC and Sponsor before use in the trial. The Investigator will retain the original of each subject's signed consent form.

DEFINITION OF END OF TRIAL

The Sponsor will make an end of trial declaration when the trial ends in an individual EU Member State and when the complete trial has ended in all participating centers in all countries within and outside the EU.

End of Trial in Member State

The End of Trial in each Member State (MS) is defined as the last subject last visit (LSLV).

End of Trial in all Participating Countries

The End of Trial will be the last subject last visit (LSLV).

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REFERENCES

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Appendix 1 – List of Abbreviations

AE	Adverse Event
ALT	Alanine Transaminase
AMI	Acute Myocardial Infarction
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate aminotransferase
BiPAP	Bilevel positive airway pressure
BMI	Body Mass Index
CFR	Code of Federal Regulations
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CRA	Clinical Research Associate
CRF	Case Report Form
CSR	Clinical Study Report
CT Scan	Computerized Tomography Scan
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
EUCTD	European Union Clinical Trial Directive
FDA	Food and Drug Administration
FEV1/FVC	Forced expiratory volume in 1 second/forced vital capacity ratio
FSFV	First subject first visit
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Process
GVHD	Graft versus Host Disease
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
i.v.	Intravenous
IB	Investigators Brochure
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IFN-ɣ	Interferon gamma
IL-1β	Interleukin-1 beta

IL-8	Interleukin-8
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web Response System
KC	Keratinocyte-derived chemokine
LAR	Legally-authorized representative
LPS	Lipopolysaccharide
LSLV	Last subject last visit
MAPC	Multipotent adult progenitor cells
mcg	Micrograms
MIP-1α	Macrophage inflammatory protein - 1 alpha
MS	Member state
NIV	Non-invasive ventilation
NSAIDS	Non-steroidal anti-inflammatory drugs
PaO2/FiO2	Arterial oxygen partial pressure/fraction inspired oxygen ratio
PEEP	Positive end-expiratory pressure
PO2	Oxygen partial pressure
PP	Per Protocol
QoL	Quality of Life
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SRM	Study Reference Manual
STEMI	ST Segment Elevation Myocardial Infarction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNF	Tumor Necrosis Factor
UC	Ulcerative colitis
UK	United Kingdom
USA	United States of America
VEGF	Vascular endothelial growth factor
WBC	White Blood Cell
WHO	World Health Organization

Appendix 2 – Definitions and Management of Infusion-Related Reactions

In the event of infusion-related reactions, Investigators should institute treatment measures according to best medical practice. Any event of infusion-related reaction, generally defined as clinically significant deviations in blood pressure, heart rate, respiratory rate and oxygen saturation, will be recorded.

In the event of infusion-related allergic reaction and if flushing, sudden rash, or difficulty breathing occur, the infusion will be stopped immediately and affected subjects will be monitored until the infusion-related allergic reaction has resolved.

The following treatment guidelines may be employed at the discretion of the treating physician:

Grade 1 infusion-related reaction (NCI-CTCAE v4.0): Mild transient reaction; infusion interruption not indicated; intervention not indicated.

Grade 2 infusion-related reaction (NCI-CTCAE v4.0): Therapy or infusion interruption indicated, but responds promptly to symptomatic treatment (e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.

1. Decrease infusion rate by 50%, administer antihistamines, corticosteroids, etc. as medically indicated and monitor for worsening condition.
2. Stop infusion if infusion-related symptoms continue despite #1.
3. Administer bronchodilators, oxygen, antihistamines, corticosteroids etc., as medically indicated.
4. Resume infusion at 50% of previous rate once reaction has decreased to Grade 1 in severity. Monitor closely for any worsening.
5. If the reaction reoccurs, stop infusion. Study treatment will be discontinued.

Grade 3 infusion-related reaction (NCI-CTCAE v4.0): Characterized as prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.

Grade 4 infusion-related reaction (NCI-CTCAE v4.0): Characterized as life-threatening consequences; urgent intervention indicated.

Treatment of Grade 3 or Grade 4 infusion-related reactions:

1. Stop the infusion immediately and disconnect infusion tubing from the subject.
2. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc. as medically indicated.
3. Immediately contact Medical Monitor and report SAE.
4. Study treatment will be discontinued.

Appendix 3 – Quality of Life Questionnaire EQ-5D

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities*)

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

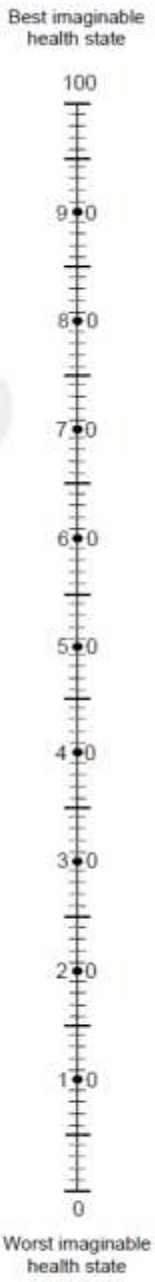
I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

SAMPLE

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Sample

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