**Specification for Contracted Services for PV**

(A Clinical Trial for a Cell Therapy Investigational Medicinal Product in Patients with Acute Respiratory Distress Syndrome)

1. **Objectives**

To procure the following:

* Pharmacovigilance (PV) management services for a phase 1/2 clinical trial.
1. **Background**

Acute Respiratory Distress Syndrome (ARDS) is a common clinical condition and a major cause of morbidity and mortality in the critical care setting. Any underlying pulmonary trauma can potentially lead to ARDS; inflammation secondary to infection, tumour or generalised sepsis; iatrogenic damage secondary to drug toxicity; pulmonary involvement in systemic diseases such as autoimmune disorders. Onset of disease typically occurs within 24-72 hours of the original illness or injury. No drug treatment exists for ARDS.

The Cell Therapy Catapult (CTC) is managing the conduct of a clinical trial to test the early safety and efficacy of a cell therapy product in patients with ARDS. The trial Sponsor is Athersys Inc. who are in collaboration with the CTC under Innovate UK funding.

The Cell Therapy Investigational Medicinal Product (CTIMP) will be administered as a single dose intravenous infusion. Patients are expected to remain in the critical care unit and as a hospital in-patient for a significant period following infusion and remain on the study, regardless of discharge, for up to a maximum period of 12 months.

The study will be conducted in 3 sequential cohorts commencing with 2 open-label cohorts (3 subjects each) allowing a single dose-escalation step followed by a randomized, double-blind, placebo-controlled cohort (30 randomized subjects). The safety data from the trial will be reviewed by an independent Data Safety Monitoring Board (DSMB). 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. A diagram of the study design is shown in **Figure 1**.

There will be approximately 8 investigational sites in the UK and 2 sites in the USA. The overall study duration from the time of first patient first visit until database lock will be approximately 2 ½ years.

Data to be collected during the study include adverse events, vital signs, safety laboratories, respiratory measures, exploratory blood biomarkers, hospitalisation data (number of days in ICU, days as in-patient, and days on ventilator). See **Figure 2** for a detailed scope of collected data.

The DSMB will convene on approximately 4 occasions to review interim, unblinded safety data. Further meetings may be scheduled on an ad hoc basis.

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 unblinding of the data prior to analysis. This early readout will be for the purpose of future clinical trial planning with an interim clinical study report (iCSR) 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.



**Figure 1.** Schematic illustration of the study design

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Day | -4 to -1 | 0Pre-infusion | 0Post-infusion | 1a | 2a | 3a | 7b  | 28c(±3 days) | 90d(±3 days) | 365d(±7 days) |
| Procedure | Screening | Baseline | Follow-up | End of Trial |
| Informed Consent | X |  |  |  |  |  |  |  |  |  |
| Inclusion/Exclusion | X | X |  |  |  |  |  |  |  |  |
| Demographics | X |  |  |  |  |  |  |  |  |  |
| Physical Exame | X | X |  |  |  | X | X | X |  |  |
| Medical History | X |  |  |  |  |  |  |  |  |  |
| Biochemistry/Hematology | X | X |  | X | X | X | X |  |  |  |
| Respiratory Function | X | X |  | Xf | Xf | Xf | Xf | Xf |  |  |
| Pregnancy test | Xg |  |  |  |  |  |  |  |  |  |
| 12-Lead ECG | X |  |  |  |  |  |  |  |  |  |
| Randomization |  | X |  |  |  |  |  |  |  |  |
| Vital Signs | X | Xh | Xi | X | X | X | X |  |  |  |
| Pre-infusion stability (2hr)j |  | X |  |  |  |  |  |  |  |  |
| IMP administration |  |  | X |  |  |  |  |  |  |  |
| Blood Sample for Exploratory Biomarkersk |  | X |  | X | X | X | X |  |  |  |
| Hospitalization Data Collectionl |  |  |  |  |  |  |  | Xm |  |  |
| Adverse Events | X |  | X | X | X | X | X | X | X | X |
| Mortality |  |  | X | X | X | X | X | X | X | X |
| Concomitant Medications | X | X | X | X | X | X | X | Xn | Xn | Xn |
| a Measurements for vital signs, biochemistry, hematology 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 Clinic visit to have a physical examination and respiratory function test if the subject is discharged from hospital prior to Day 28.d Data to be collected by telephone call.e Physical exam to include at least general appearance, cardiovascular, respiratory, skin, lymph nodes, abdomen.f Only if subject is on a ventilator; to include rate, tidal volume and airway pressures (peak and plateau) plus mode of ventilation including PaO2/FiO2 and PEEP.g 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.h Vital signs including blood pressure, pulse, respiration, pulse oximetry and temperature will be collected 1 hour ± 30 minutes prior to infusion start.i Vital signs including blood pressure, pulse, respiration, pulse oximetry and temperature will be collected every 15 ± 5 min for the first 2 hours and at 4 hours ± 30 minutes after infusion start.j 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 patient is still within the 96-hour window: (a) PEEP ≥20 cm H2O (b) a change, positive or negative, in PaO2/FiO2 ratio of 15% relative to the start of the 2-hour pre-infusion stability period;  (c) requires addition of a third vasopressor or a rise of 10 mcg or more in current dose of vasopressors (d) requires use of >0.1 mcg/kg/min epinephrine for blood pressure support.k Exploratory blood analyses will include the measurement of total white blood cell count, absolute neutrophil count and inflammatory cytokine biomarkers at baseline (Day 0 Pre-Infusion) and Days 1, 2, 3 and 7.l Includes Ventilator Free Days, Hospitalization Days and ICU Days.m Hospitalizationdata will be collected through to Day 28, as described in Section 7.1. n Reported for medications given for treatment of adverse events. |

**Figure 2.** Schedule of Activities (from protocol)

1. **Assumptions**
* Experience in critical care phase I/II safety studies, and ideally in ARDS or related inflammatory lung conditions.
* EU and FDA compliance
* The role requires a drug safety manager with appropriate qualifications and experience (dedicated manager for the duration of the study)
* Management includes US sites
1. **Expectations**

Attendance to weekly study team meetings (teleconference), attend an investigator meeting (UK) where the key individual will be likely required to prepare and present the relevant study material (e.g. SAE reporting).

Training of US sites will be conducted via webinar.

1. **Timelines and Scope**

|  |  |
| --- | --- |
| Number of subjects screened | Approx. 80 |
| Number of subjects randomised | 36 |
| Number of sites | Approx. 8 in UK and 2 in US |
| Recruitment period | 18 months |
| DB go live | Aug 2015 |
| FPFV | Sep 2015 |
| LPLV | Dec 2017 |
| Database hard lock | Jan 2018 |

**Scope of Services:**

|  |  |
| --- | --- |
| **Description** | **Assumption / Comment** |
| **Safety / Medical Monitoring** |
| **General** |  |
| * Prepare safety/PV plan
 | Yes |
| **SAE Handling/Reporting** |  |
| * Process SAEs
 | Yes |
| * Number of SAEs processed (includes site contact)
 | 1 per patient |
| * Reconcile SAEs with clinical database
 | No(Task to Data Manager) |
| **SAE Narratives** |  |
| * Write brief SAE narratives
 | Yes |
| **Safety Alert Letters** |  |
| * Compose safety alert/IND letters to Investigators
 | Yes |
| * Distribute safety alert/IND letters to Investigators
 | No (Task to Cell Therapy Catapult) |
| * Distribute safety alert/IND letters to Regulatory Authorities/Central IRBs/ECs
 | No (Task to Sponsor [Reg] / Cell Therapy Catapult [EC]) |
| **Single Case Reporting** |  |
| * Prepare single case reports to Regulatory Authorities
 | Yes |
| * Number of expected single case SUSAR reports
 | 2 |
| **Periodic or Annual Reporting** |  |
| * Prepare SAR listing for annual safety report according to Directive 2001/20/EC
 | Yes |
| * Prepare DSUR (2016)
 | Yes |
| * Submit DSUR
 | Yes |
| **DSMB Reporting** |  |
| * Prepare listings for DSMB
 | Yes |
| * Estimated number of DSMB meetings
 | 4 |
| **Safety Reviews** |  |
| * Conduct safety reviews
 | Yes |