Clinical Trial Protocol: ImmunoFolate for the Treatment of ARDS

Title:
A Phase 2 Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Safety and Efficacy of ImmunoFolate in Patients with Acute Respiratory Distress Syndrome (ARDS)

1. Background and Rationale

ARDS is a severe, life-threatening condition characterized by widespread inflammation in the lungs. ImmunoFolate, a novel pterin-based immunoregulatory compound, has been shown to modulate cytokine production (notably IL-12, IFN-γ upregulation and TGF-β downregulation) in preclinical studies, potentially reducing cytokine storm and improving pulmonary function in ARDS.

---

2. Objectives

Primary Objective:

- To evaluate the efficacy of ImmunoFolate in improving the PaO2/FiO2 ratio in patients with moderate-to-severe ARDS.

Secondary Objectives:

- To assess mortality at Day 28 and Day 90.
- To measure time on mechanical ventilation.
- To evaluate ICU and hospital length of stay.
- To assess inflammatory biomarkers (IL-6, TNF-α, IFN-γ, CRP).
- To assess safety and tolerability.

---

3. Study Design

- **Type:** Randomized, double-blind, placebo-controlled
- **Phase:** 2
- **Centers:** Multi-center (optional depending on sponsor capacity)
- **Subjects:** 100 patients with confirmed ARDS
- **Randomization:** 1:1 (ImmunoFolate vs. placebo)
- **Blinding:** Double-blind
- **Duration:** 28-day treatment + 90-day follow-up

---

4. Inclusion Criteria

- Age 18–80
- Diagnosis of ARDS per Berlin Criteria
- PaO2/FiO2 ≤ 200 mmHg
- On mechanical ventilation ≤ 48 hrs at time of enrollment
- Informed consent from patient or legally authorized representative

---

5. Exclusion Criteria

- Known hypersensitivity to folates or pterins
- End-stage chronic illness with life expectancy < 3 months
- Pregnancy or lactation
- Active malignancy undergoing treatment
- Immunosuppressive therapy within past 3 months
- Participation in another interventional trial within 30 days

---

6. Investigational Product

Name: ImmunoFolate
Formulation: Oral or IV (depending on pharmacokinetic data availability)
Dose: [To be determined from PK/PD studies or starting with 5 mg/day if oral; IV loading dose may be 1 mg/kg followed by maintenance]

---

7. Treatment Plan

- **Arm A:** ImmunoFolate once daily x 10 days or until extubation, whichever is sooner
- **Arm B:** Placebo (matched) once daily x 10 days or until extubation
- Concomitant therapies per standard of care allowed

---

8. Outcome Measures

Primary Endpoint:

- Change in PaO2/FiO2 ratio from baseline to Day 7

Secondary Endpoints:

- Mortality at Day 28 and Day 90
- Ventilator-free days at Day 28
- Change in inflammatory markers from baseline to Day 7
- ICU and hospital length of stay
- Adverse event rate

---

9. Statistical Analysis

- **Sample Size Calculation:** Based on effect size of 30 mmHg improvement in PaO2/FiO2 with SD of 50 mmHg, $\alpha = 0.05$, power = 80%
- **Primary Analysis:** ANCOVA adjusting for baseline PaO2/FiO2
- **Secondary Analyses:** Kaplan-Meier for survival, t-tests or non-parametric equivalents for continuous outcomes
- **Safety Analyses:** Descriptive statistics; adverse events compared using Fisher's exact test

---

10. Ethics and Regulatory

- Conducted per ICH-GCP
- IRB/Ethics Committee approval required prior to enrollment
- Written informed consent mandatory
- Data Monitoring Committee (DMC) to oversee safety

---

11. Data Management and Monitoring

- Electronic Data Capture system
- Source data verification
- Independent DMC for interim safety reviews
- Protocol deviations and adverse events documented per FDA and sponsor guidelines

---

12. Potential Risks and Benefits

Risks:

- Unknown side effects, possible immune suppression or over-activation

Benefits:

- Potential to reduce inflammation, improve oxygenation, and enhance survival in ARDS

---

13. Timeline

- **Start-up/Regulatory:** 3 months
- **Enrollment period:** 6–9 months
- **Primary endpoint completion:** 1 month post last patient enrolled
- **Final study report:** within 3 months of last patient last visit

---