# A Phase 3, Multicenter, Double-blind, Placebo Controlled Study of an Anti-TLR4 Antibody, Paridiprubart, in Adult Patients With Respiratory Distress on Invasive Mechanical Ventilation

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# Disclosure to Learners

**Financial Relationships with “ineligible companies” within the past 24 months:**

- Edesa Biotech, Inc. – Consultant, travel support

# TLR4 Activation and Critical Illnesses

## Multiple insults can lead to ARDS through TLR4 activation—Most critically ill patients are managed similarly

**Inducing Agent/Insult**

**Bacterial**
(e.g. gram-negative)

**Viral**
(e.g. Influenza, SARS-CoV2)

**Chemical**
(e.g. Acid, chemical weapons)

**Endogenous**
(e.g. HMGB1, calprotectin)

**Ventilator-induced**

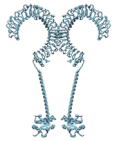
**CBRN-relevant**

CBRN: Chemical, biological, radiological and nuclear defense

**Host Damage Response (DAMPs)**

- **Acute Respiratory Distress Syndrome**
- Acute Kidney injury
- Multi-organ failure
- Pneumonia
- Sepsis

Death



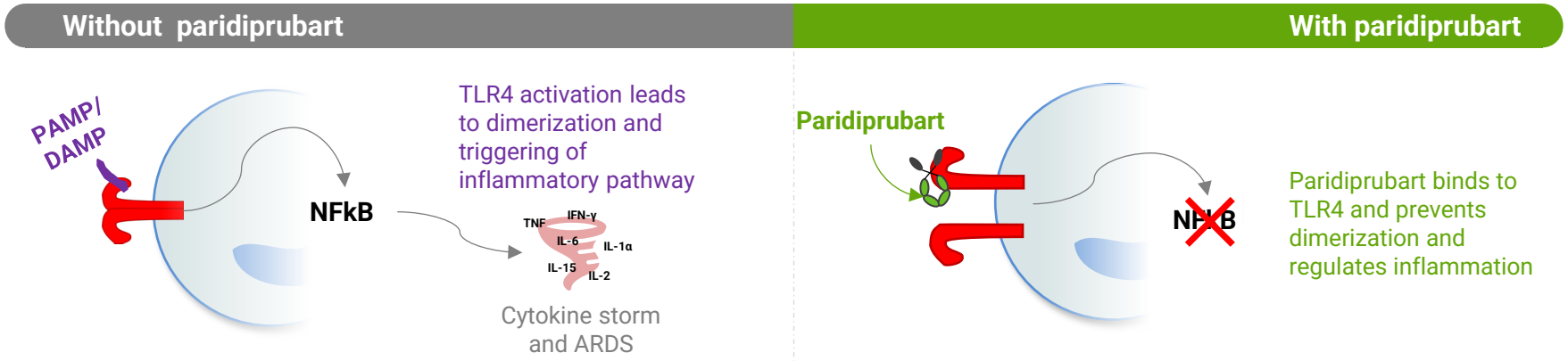
Sustained TLR4 Activation

**Paridiprubart's Target**

**Paridiprubart is a threat-agnostic therapy** that can modulate harmful, dysregulated immune responses resulting from multiple insults.

# Overview of Paridiprubart – Initial focus on ARDS

## Paridiprubart is an anti-TLR4 monoclonal antibody that dampens the dysregulated immune response in ARDS




**Mechanism of Action**

- Paridiprubart binds to toll-like receptor 4 (TLR4) with high specificity and high affinity, in a ligand-independent manner.
- It helps alleviate the dysregulated damage/immune response that leads to ARDS, irrespective of the initial stimulus.

**Dose, Route of administration**

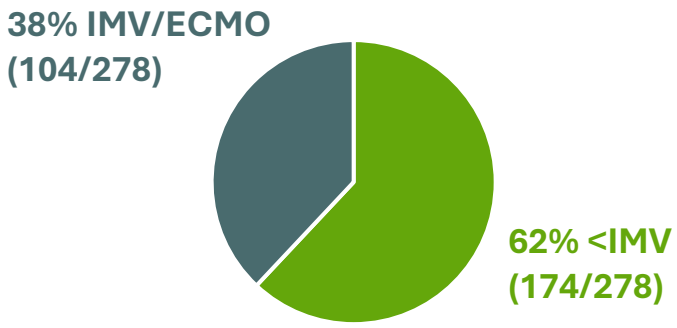
- A 15 mg/kg single dose i.v. infusion was calculated from extensive PK/PD modelling and simulation of phase 1 data in HV. Dose is estimated to maintain a concentration sufficient for pharmacological effect (99% inhibition of IL-6 and CXCL10 for ≥4 weeks).

# Phase 3 Study Design

## Intent to treat population comprised of 104 patients on IMV

**ITT Population (IMV with or without ECMO/Organ Support)**


**Safety Population (with or without IMV)**




138 Paridiprubart, 140 Placebo

### Key Inclusion Criteria

- Men and women >18 years old
- Positive COVID-19 test
- Negative pregnancy test
- IMV

### Key Exclusion Criteria

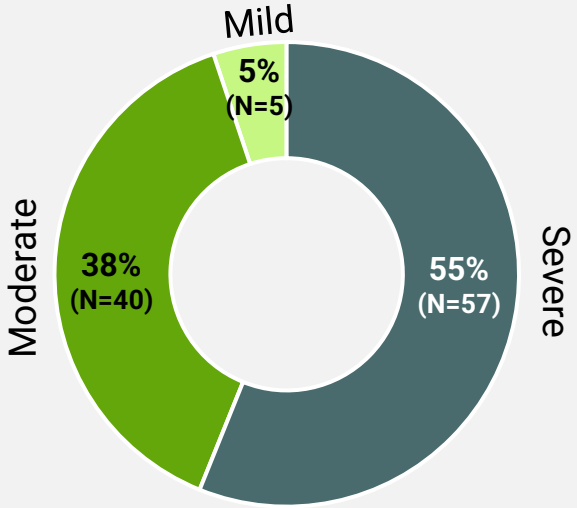
- Pregnant or breastfeeding women
- Progression to death within 48-72h is imminent/inevitable
- Active participation in immunomodulator trials
- Treatment with immunosuppressant drugs that are not part of SOC
- Meaningful clinical improvement prior to administration

# Phase 3 Baseline Characteristics

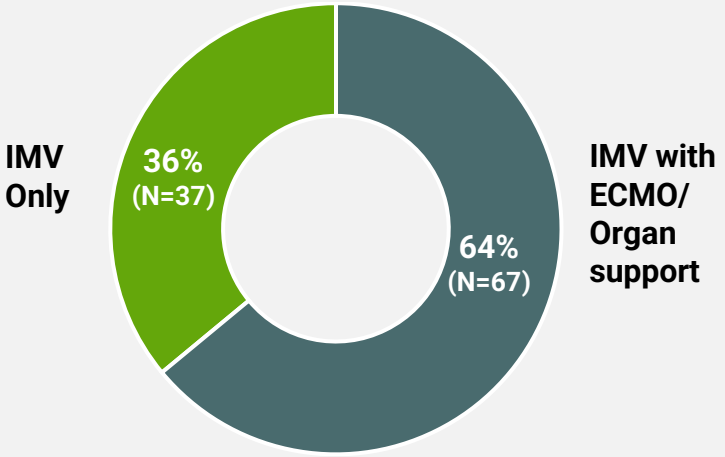
## Intent to treat population comprised of 104 patients on IMV

### Average Age


### ARDS Severity



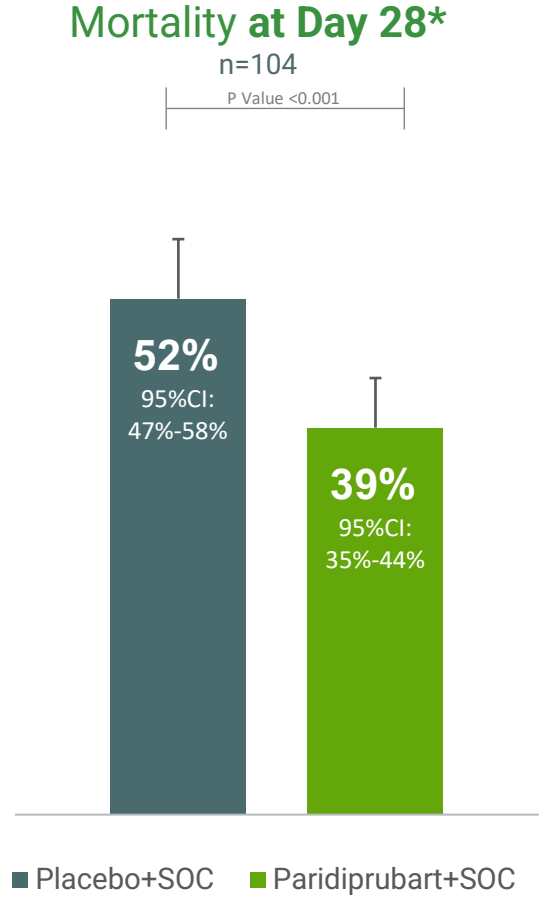

### Clinical Severity

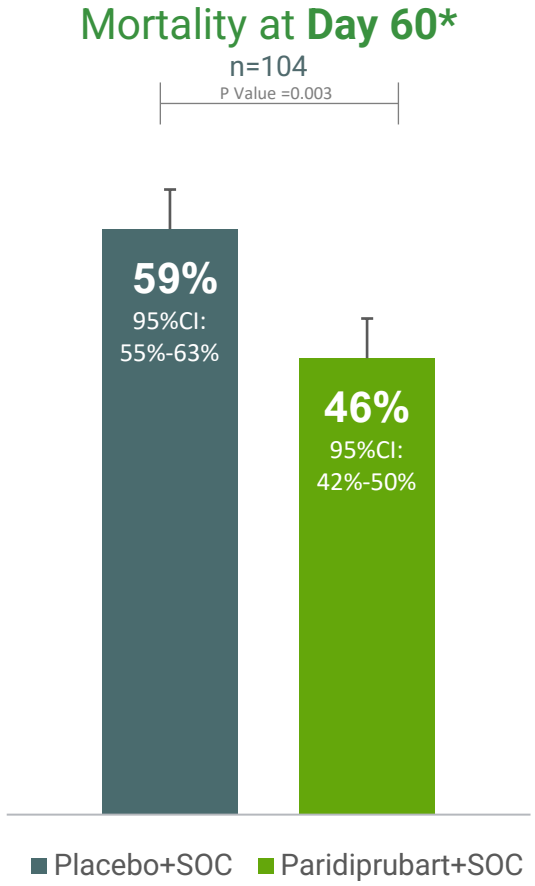



| | Paridiprubart | | Placebo | | Total | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| **Antivirals** | 4 | 7.1% | 6 | 12.5% | 10 | 9.6% |
| **Corticosteroids** | 25 | 44.6% | 21 | 43.8% | 46 | 44.2% |
| **Immunomodulators** | 6 | 10.7% | 4 | 8.3% | 10 | 9.6% |

# Phase 3 Results – Primary Endpoint 28-Day Mortality

## Paridiprubart Met Primary and Secondary Endpoints with Statistical Significance




* Estimated risk of mortality using multivariate logistic regression derived risk differences (95% confidence interval). Final Phase 3 protocol comprised ICU patients with ARDS (mild/moderate/severe); Invasive Mechanical Ventilation and/or patients receiving organ support/ECMO; Company opted to truncate enrolment for business reasons: 104 Patients enrolled in intention-to-treat; 278 patients (safety ITT). Subject randomized 1:1 placebo plus standard of care (SOC) treatment or paridiprubart + SOC.

## Summary of Phase 3 Results

**28-Day Mortality Rate:** Paridiprubart had a relative reduction in the risk of death of 25% compared to placebo

**60-Day Mortality Rate:** A durable survival benefit was also demonstrated. Paridiprubart had a relative reduction in the risk of death of 22% vs. placebo

**Clinical Improvement at Day 28:** Paridiprubart showed a 41% higher relative rate of clinical improvement, meaning patients no longer required IMV and/or organ support

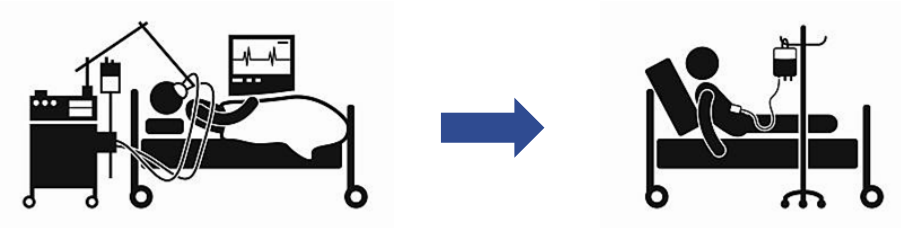
**Other Signals:** Paridiprubart reduced mortality in a population that included patients not on IMV

**Safety Population**: Favorable safety profile in 278 subjects

# Paridiprubart Treatment Had Significant Impact on Clinical Improvement

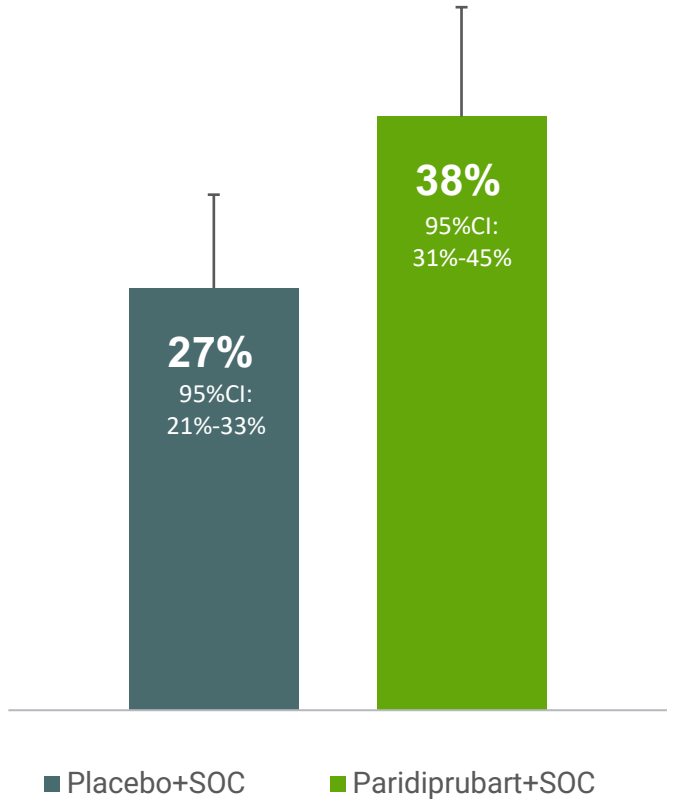
## Treatment Nearly Doubled the Chance of Recovery by Day 28 - ITT

**Secondary Endpoint**
Proportion of Patients Who Achieved at Least a 2-Point Reduction in the WHO scale.



**Implies that patients are no longer in the ICU requiring invasive mechanical ventilation and organ support at Day 28**

**Estimated Proportion Achieving a 2-pt Reduction in WHO Scale (p=0.032)**




Patients Treated with Paridiprubart Had a Significantly Higher Likelihood of Being Free from Mechanical Ventilation and Organ Support by Day 28 Compared to Placebo

# Safety Assessment

## Paridiprubart exhibits a favorable safety profile

| Parameter | Treatment Group | | | |
|---|---|---|---|---|
| | EB05 (N=138) | | Placebo (N=140) | |
| | N of Event | Patients (%) | N of Event | Patients (%) |
| **Overall** | 732 | 111 (80.4%) | 682 | 118 (84.3%) |
| **Severity, n (%)** | | | | |
| Mild | 380 | 94 (68.1%) | 335 | 97 (69.3%) |
| Moderate | 221 | 70 (50.7%) | 235 | 80 (57.1%) |
| Severe | 130 | 61 (44.2%) | 112 | 60 (42.9%) |
| **Serious, n (%)** | 138 | 64 (46.4%) | 120 | 63 (45.0%) |
| Death | 45 | 45 (32.6%) | 49 | 49 (35.0%) |
| Persistent Disability | 5 | 5 (3.6%) | 4 | 4 (2.9%) |
| Prolongation of Hospitalization | 25 | 17 (12.3%) | 25 | 17 (12.1%) |
| Life Threatening | 54 | 29 (21.0%) | 49 | 35 (25.0%) |
| Medically Important | 47 | 19 (13.8%) | 37 | 27 (19.3%) |
| **Relationship to study drug, n (%)** | | | | |
| Definitely | 0 | 0 (0.0%) | 1 | 1 (0.7%) |
| Probably | 2 | 2 (1.4%) | 8 | 3 (2.1%) |
| Possibly | 25 | 14 (10.1%) | 20 | 10 (7.1%) |
| Unlikely | 126 | 33 (23.9%) | 105 | 31 (22.1%) |
| Not related | 579 | 99 (71.7%) | 548 | 99 (70.7%) |
| **Outcome, n (%)** | | | | |
| Fatal | 45 | 45 (32.6%) | 49 | 49 (35.0%) |
| Not recovered (continuing) | 289 | 66 (47.8%) | 296 | 76 (54.3%) |
| Recovered with sequelae | 13 | 11 (8.0%) | 20 | 12 (8.6%) |
| Recovered without sequelae | 312 | 80 (58.0%) | 234 | 83 (59.3%) |
| Unknown | 23 | 14 (10.1%) | 33 | 9 (6.4%) |
| Improving | 37 | 20 (15.2%) | 44 | 18 (12.9%) |

Patients may have experienced more than one adverse event.
Number of events leading to death were collapsed per patient.

- Safety population for the phase 3 study consisted of 278 patients (138 with EB05 and 140 with placebo).
- A total of 464 patients and healthy volunteers have been dosed with paridiprubart over the course of its development history, validating a favorable safety profile.

Data extracted from a draft clinical study report; may be subject to change prior to final report.

# Conclusions

**As a result of the phase 3 study, Paridiprubart has demonstrated:**

- ✓ **Success in meeting primary & secondary endpoints** with statistically significant reductions in 28- and 60-day mortality.
- ✓ **Improved clinical recovery**: higher rate of 2-point WHO improvement and earlier liberation from IMV/organ support.
- ✓ **Favorable safety profile** in 278 treated patients.