Clinical Development of EB05 for the Treatment of ARDS

ARDS Drug Development Summit
July 14, 2022
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Note: All financial and share price information is presented in U.S. dollars.
Agenda

01 Introduction: Company Overview
02 TLR4 as a Therapeutic Target for ARDS
03 EB05 as a Therapeutic Agent
04 Clinical Development
Edesa is a Clinical-Stage Company
Building on Established Efficacy and Safety in Multiple Indications

- Two Later Stage, Validated Technologies
  - Potentially First-in-Class Drug Therapies
  - Address Large Market Opportunities

- Building on Positive Results
  - Positive interim data
  - Upcoming completion of two studies

- Entrepreneur CEO with Multiple Successful Start-ups and Exits
  - Expertise in identifying validated assets with efficient development paths
# Edesa’s Development Pipeline

<table>
<thead>
<tr>
<th>Drug Candidates</th>
<th>Indications</th>
<th>Pre-Clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Status/Milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>EB05</td>
<td>Anti-TLR4 mAb, ARDS and Other Indications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive Ph2 Results; Health Canada Approved Ph3 Design</td>
</tr>
<tr>
<td>EB01</td>
<td>Allergic Contact Dermatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive Blinded Interim Results; Enrollment by Q4*</td>
</tr>
<tr>
<td>EB02</td>
<td>Hemorrhoids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CTA Approved – PoC Study</td>
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<tr>
<td>EB06</td>
<td>Anti-CXCL10 mAb, ARDS and Other Indications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Growth Opportunities</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>Vitiligo</td>
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<td>Producing mAbs for Novel Targets</td>
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* Company Press Release 4/28/2022
Edesa’s Target: Toll-Like Receptor 4 (TLR4)

TLR4’s role in innate immunity is well established

- Pivotal to inception of innate immune response; subject of the Nobel Prize in 2011.
- Expressed on activated macrophages and neutrophils.
- Activated by several PAMPs and DAMPs, playing a key role in numerous conditions.
- Substantial evidence that multiple causes of ARDS are mediated by the TLR4 pathway
  - Key actor on the DAMPs-driven self-amplifying dysregulated response that leads to ARDS.
  - Recent data shows that SARS-CoV-2 spike protein activates TLR4*.

* https://www.biorxiv.org/content/10.1101/2020.12.18.423427v1
DAMPs and Severity of COVID-19
Calprotectin and HMGB1 strongly correlated with severity

High levels of DAMPs → Poor Outcomes

High levels of S100A8/A9 (Calprotectin) and HMGB1 were associated with disease severity and poor outcomes.

Blocking Calprotectin/TLR4 → Improved Survival

Inhibition of S100A8/A9-TLR4 axis led to 100% survival in a coronavirus mouse model.

Sources: https://doi.org/10.1038/s41423-020-0492-x; Guo et al., 2021, Cell Host & Microbe 29, 1-14;
TLR4 Inhibition to Treat Viral Infections
Multiple Animal Studies Demonstrate the Importance of TLR4 in Immune Response

1. Mice lacking TLR4 are **protected from lethal influenza** infections
2. TLR4 inhibition **suppresses expression** of various cytokines
3. Anti-TLR4 mAb **protects mice against lethal** influenza


Anti-TLR4 IgG = TLR4 Antagonist
Management of COVID-19
Current Treatment Paradigm

Non-Hospitalized
- Vaccines
- Monoclonal Antibodies

Hospitalized
- Suppl. Oxygen
- Invasive Mechanical Ventilation (IMV)
- IMV with organ support and/or ECMO

High Unmet Medical Need: EB05 Initial Target Populations

Viral Infection Phase
Inflammatory Phase

Mild
Death

Viral Infection Phase
Inflammatory Phase

Vaccines
Monoclonal Antibodies
Antivirals
Remdesivir
EB05
Dexamethasone
Tocilizumab

ECMO = Extracorporeal membrane oxygenation
EB05

Anti-TLR4 mAb for treatment of Acute Respiratory Distress Syndrome associated with COVID-19

- **Novel mechanism of action** based on blocking of TLR4 receptors.

- in vitro, in vivo and human data supporting EB05’s ability to block TLR4.

- Approximately 300 patients in Phase 1 and 2 trials with no significant AEs.

- Ongoing Phase 2/3 adaptive clinical trial in multiple jurisdictions.
EB05 – Potential Best in Class Anti-TLR4 mAb
Potential to target indications that involve dysregulated innate immunity

Without EB05

TLR4 activation leads to dimerization and triggering of inflammatory pathway

NFkB

PAM/ DAMP

EB05 binds to TLR4 and prevents dimerization and regulates inflammation

With EB05

NFkB

Cytokine storm and ARDS

Binds to TLR4 with high specificity; ligand independent

Single IV Infusion

>10 years of preclinical and clinical efficacy and safety work

Multiple successful GMP runs

EB05 binds to TLR4 and prevents dimerization and regulates inflammation
EB05 (5E3) inhibits neutrophil recruitment and cytokine expression in lung

**EB05 blocked the recruitment of neutrophils to the lung in a dose-dependent and saturable manner**

**EB05 blocks IL-6 and TNFα- (and RANTES) accumulation in the BAL fluid in a dose-dependent and saturable manner**

BAL = bronchoalveolar lavage;
Highlighted Clinical Studies
LPS Challenge – Healthy Volunteers

EB05 (0.25 mg/Kg)

Day 0  →  Day 1  →  Day 22  →  Day 40

1. Volunteers administered with LPS, a key marker of bacterial infection
2. Levels of certain cytokines measured at regular time intervals from administration (up to 10 hours)
3. Test repeated at days 22 and 40.
Evidence of Activity in Humans
EB05 Inhibited “Cytokine Storm” after *In Vivo* LPS Challenge

A single low dose provided a measurable protective response to the LPS challenge for more than 22 days. At Day 40, response returning to normal.
Evidence of Activity in Humans
EB05 Lowered Fever and Stabilized Vital Signs after *In Vivo* LPS Challenge

A single low dose blocked fever by more than 1 degree Celsius and maintained heart rate during LPS challenges for more than 22 days. At Day 40, response returning to normal.

Good safety profile in HV: Up to 15mg/kg tested as a single dose and 5mg/kg in repeat dose studies.
The Phase 2 Design Covered a Wide Range of Disease Severity Levels

The first stage of the Phase 2/3 trial was designed to cover a wide range of patient populations across COVID-19 and ARDS severities.

The KEY goal was to identify which populations/signals should be the focus of the Phase 3.

<table>
<thead>
<tr>
<th>WHO COVID-19 Severity Scale</th>
<th>Description</th>
<th>Standard of care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 4</td>
<td>Hospitalized requiring supplemental Oxygen</td>
<td>Remdesivir, dexamethasone (Dex) preferably in combination with remdesivir</td>
</tr>
<tr>
<td>Level 5</td>
<td>Hospitalized requiring high-flow Oxygen Delivery or Non-invasive ventilation</td>
<td>Dex, or Dex in combination with remdesivir, Baricitinib or tocilizumab (Toci) can be used in combination with the above in certain cases.</td>
</tr>
<tr>
<td>Level 6</td>
<td>Hospitalized requiring invasive mechanical ventilation (IMV)</td>
<td>Dex plus Toci. Sarilumab may be used, if Toci is not available.</td>
</tr>
<tr>
<td>Level 7</td>
<td>Hospitalized requiring extracorporeal membrane oxygenation (ECMO) and/or IMV with additional organ support</td>
<td>Dex and Toci likely used and all treatment options exhausted.</td>
</tr>
</tbody>
</table>

Level 7 patients are among the most significant unmet needs in COVID-19
**EB05 Clinical Trial Design**

**Phase 2 Population**

**Inclusion:**
- Men and women ≥18 years of age
- COVID-19 diagnosis
- Hospitalized for COVID-19 respiratory disease
- Patient belongs to Levels 3-6 in the nine-point COVID-19 severity scale (Main Study) or Level 7 (Critically Ill)
- For women of childbearing potential neg. pregnancy test
- Signed informed consent form

**Exclusion:**
- The subject is breastfeeding or pregnant.
- Known hypersensitivity to EB05 or its excipients.
- Death is imminent and inevitable within the next 48 - 72 hours, irrespective of the provision of treatment.
- Active participation in other drug clinical trials.
- Treatment with immunomodulator or immunosuppressant drugs unless it is part of SOC
- Known other clinical conditions that contraindicate EB05 and cannot be treated or solved according to the judgment of the clinician.

**Phase 2 Clinical Trial Design**

- **Main Study (Level 3-6)**
  - Placebo (N=157)
  - EB05 (N=162)
- **Critically Ill (Level 7)**
  - Placebo (N=19)
  - EB05 (N=14)

**DSMB Review**

**Phase 3**

- **Level 6 Cohort**
  - Invasive Mechanical Ventilation
  - ~500 Evaluable Subjects
- **Level 7 Cohort**
  - Critically ill
  - ~315 Evaluable Subjects
### Summary of Results

#### Baseline Characteristics

<table>
<thead>
<tr>
<th>COVID-19 Scale</th>
<th>ARDS Criteria</th>
<th>N</th>
<th>Signal Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECMO and/or IMV with Add. Org. Supp. (Level 7)</td>
<td>Mild to Severe</td>
<td>33</td>
<td>28-day mortality:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 14.3% (2/14) for EB05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 36.8% (7/19) for Placebo;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• <strong>Hazard Ratio</strong> = 3.17 (p=0.15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Odds ratio = 3.50 (p=0.16)</td>
</tr>
<tr>
<td>Supp. Oxygen (Level 4)</td>
<td>Severe</td>
<td>26</td>
<td>28-day mortality:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 16.7% (2/12) for EB05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 42.9% (6/14) for placebo;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• <strong>Hazard Ratio</strong>: 2.94 (p=0.19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Odds ratio: 3.75 (p=0.16)</td>
</tr>
<tr>
<td>High-flow oxygenation or worse (Levels 5,6,7)</td>
<td>Mild to Moderate</td>
<td>76</td>
<td>28-day mortality:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 10.8% (4/37) for EB05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 20.5% (8/39) for placebo;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• <strong>Hazard Ratio</strong>: 2.03 (p=0.25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Odds Ratio: 2.13 (0.25)</td>
</tr>
</tbody>
</table>

**Mean difference in days alive and free of IMV**

- 6.1 more days for patients treated with EB05 versus placebo (95% CI, p<0.05)

**COVID-19 Scale:** 4 = Hospitalized requiring Oxygen supplementation; 5 = Hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both; 6 = Hospitalized Severe Disease - intubation and invasive mechanical ventilation; 7 = Extracorporeal Membrane Oxygenation (ECMO) and/or invasive mechanical ventilation with additional organ support; **Berlin ARDS Criteria:** Mild = PaO₂/FiO₂ between 200 and 300 mm Hg; Moderate = PaO₂/FiO₂ between 100 and 200 mm Hg; Severe = PaO₂/FiO₂ <100 mm Hg
Critically ill Patients (Level 7)
Baseline Characteristics

**WHO Severity Level:**
Level 7: Extracorporeal membrane oxygenation, invasive mechanical ventilation + organ support or both
Level 8: Death

- **ITT = mITT**
- **33 patients** (No Patients removed)

**Mean Age**: 46
**Age Range**: 24-62
**BMI (mean)**: 36
**Non-Caucasian**: 30%
**Corticosteroid >90%**: 67%
**IL-6 >45%**: 33%

- **Canada**
  - ECMO (85%)
  - IMV + Org Supp (15%)

- **USA**

**WHO Severity Level:**
Level 7: Extracorporeal membrane oxygenation, invasive mechanical ventilation + organ support or both
Level 8: Death
Critically ill patients demonstrated a 68.5% reduction in the risk of dying when treated with EB05 over SOC

- 28-day death rate of 14.3% (2/14) in the EB05 arm versus 36.8% (7/19) in the placebo arm in critically severe patients, primarily on ECMO therapy (Level 7).

- Survival Analysis (Cox’s Proportional Hazard Model): EB05+SOC = 68.5% reduction in the risk of dying when compared to placebo + SOC at 28 days (HR: 3.17 placebo vs. EB05; 95% CI: 0.66-15.35; p=0.15, Odds Ratio: 3.50 placebo vs. EB05; 95% CI:0.60-20.41; p=0.16).

- Mean of 7 VFD for EB05 vs. 3 VFD for Placebo over the 28 day study period
A Strong Mortality Signal was Detected

<table>
<thead>
<tr>
<th></th>
<th>Tocilizumab(^1)</th>
<th>Dexamethasone(^2)</th>
<th>EB05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Severity</td>
<td>IMV</td>
<td>IMV</td>
<td>IMV+ and/or ECMO</td>
</tr>
<tr>
<td>Mortality (Active)</td>
<td>31%</td>
<td>29%</td>
<td>14.3%</td>
</tr>
<tr>
<td>Mortality (Placebo)</td>
<td>35%</td>
<td>41%</td>
<td>36.8%</td>
</tr>
<tr>
<td>Number of Patients Required to Detect Signal</td>
<td>~4,000</td>
<td>~1,000</td>
<td>33</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>1.17</td>
<td>1.56</td>
<td>3.17</td>
</tr>
</tbody>
</table>

EB05 is the only one of these drugs to demonstrate a mortality signal in ECMO patients\(^1,2\)

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1. ‘Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomized, controlled, open-label, platform trial’, Lancet 397(2021), 1637-1645
2. ‘Dexamethasone in Hospitalized with COVID-19’, The New England Journal of Medicine, 384 (2021), 8, p 693
28-Day Mortality Data
Severe ARDS Patients on Supplemental $O_2$ (Level 4)

<table>
<thead>
<tr>
<th>Population</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>136 patients on supplemental Oxygen</td>
<td>1.523</td>
</tr>
<tr>
<td>26 patients on supplemental Oxygen with Severe ARDS</td>
<td>2.943</td>
</tr>
</tbody>
</table>

28 Day Cumulative Mortality

- Placebo
- EB05

Cumulative Mortality (%) vs Time (Days)
28-Day Mortality Data and VFDs
Patients requiring more than Supplemental O₂ (Levels 5, 6 and 7)

Population Hazard Ratio
190 patients levels 3,4,5,6 and 7 1.46
76 patients levels 5,6 and 7 2.03

All patients in this group with mild or moderate ARDS at baseline

At Day 28

<table>
<thead>
<tr>
<th></th>
<th>EB05</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>89.2% (33/37)</td>
<td>79.5% (31/39)</td>
</tr>
<tr>
<td>Deceased</td>
<td>10.8% (4/37)</td>
<td>20.5% (8/39)</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>2.03 (p=0.25)</td>
<td></td>
</tr>
</tbody>
</table>

Mean difference in days alive and free of IMV at day 28:

6.1

More days for patients treated with EB05 + SOC; (p<0.05)

VFD = Ventilator-free days (or days alive and free of IMV); IMV = Invasive mechanical ventilation
EB05 is a monoclonal antibody that blocks Toll-Like Receptor 4 (TLR4) – a key target for modulation of dysregulated inflammatory response.

TLR4 is a key mediator to the development of acute respiratory distress syndrome (ARDS) coming from a variety of causes, including sepsis, smoke and chemical inhalation, bacterial and viral infections such as influenza and SARS-CoV-2.

Ongoing Phase 2/3 study of investigational mAb in COVID-19 induced ARDS. In Sept. 2021, the company completed the Phase 2, signal-finding part of the study.

Due to strong efficacy signal for 28-day mortality endpoint in critically ill (ECMO and/or IMV with additional Organ Support), the study’s DSMB unblinded mortality endpoint and recommended continuation to confirmatory Phase 3
- 68.5% improvement in 28-day mortality for critically ill patients
- Signals for mortality and ventilator free days also detected in other populations

Company focusing on critically severe patients for Phase 3

Phase 3 enrollment is ongoing.