



TARGETING INFLAMMATION FOR ACUTE RESPIRATORY DISTRESS SYNDROME

Reparixin is an investigational drug that is not approved for use in any country and is currently being investigated in clinical trials.



KEY ARDS FACTS

ARDS is a complex, heterogeneous disease with a mortality rate that may exceed **40%**.¹¹

The heterogeneity of ARDS most likely contributes to the poor clinical outcomes seen for this condition.¹²

A subset of patients with ARDS may be classified as having a hyperinflammatory phenotype owing to the presence of higher levels of inflammatory biomarkers and cytokines (such as IL-8); this population may benefit from a more targeted approach, such as anti-inflammatory therapy (ie, precision medicine).^{4,13}

The current standard of care for ARDS focuses on management of symptoms by improving oxygenation and maximizing respiratory system compliance.^{14,15}

Ventilatory management is a supportive technique that does not address the physiologic mechanism that underlies ARDS, including the role of inflammation in acute lung injury.^{2,13} Treatments that target hyperinflammation to prevent disease complications remain an unmet need.^{2,13}

ARDS BACKGROUND

Acute respiratory distress syndrome (ARDS) is an acute inflammatory lung injury characterized by increased pulmonary vascular permeability and substantial impairments in gas exchange associated with hypoxemia and bilateral pulmonary opacities on chest radiography.^{1,2} According to the Berlin criteria, ARDS can be classified on the basis of hypoxemia severity: mild (PaO₂/FiO₂ of 201-300 mmHg), moderate (PaO₂/FiO₂ of 101-200 mmHg), or severe (PaO₂/FiO₂ ≤100 mmHg).¹

ARDS can develop from direct injury or indirect inflammatory injury; common etiologies of ARDS include sepsis, pneumonia, aspiration, and trauma-associated shock.^{3,4} Identifying the cause of ARDS is an important factor in precision medicine, as some etiologies are associated with more severe illness and worse outcomes.⁴

After pulmonary injury, development of ARDS involves the recruitment of multiple inflammatory cell types that mediate tissue damage; this infiltration, along with persistent inflammation, can result in respiratory failure, causing the need for intensive care unit (ICU) admission and mechanical ventilation and increasing the risk of mortality.⁵⁻⁷

Early in the disease course, activated alveolar macrophages recruit neutrophils into the lungs; excessive accumulation of neutrophils leads to alveolar pathology, including tissue damage and pathological alveolar-capillary permeability.^{2,5,8}

Activated neutrophils play a central role in the development and severity of ARDS through the release of chemokines, specifically interleukin (IL)-8 (also known as CXCL8); neutrophils can also release other toxic mediators, including reactive oxygen species and neutrophil extracellular traps (NETs), which can lead to epithelial injury.^{2,9,10}



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DOMPÉ IS INVESTIGATING IF INHIBITION OF IL-8 SIGNALING CAN LIMIT ARDS-MEDIATED LUNG INJURY.

Development and severity of ARDS are directly related to the presence of neutrophil activity in the lungs; IL-8, which binds to cellular receptors CXCR1 and CXCR2, is involved in the recruitment, activation, and degranulation of these cells and therefore contributes to inflammation amplification.^{2,16,17}

In response to triggers such as injury or infection, neutrophils, activated by IL-8, form NETs, which are extracellular fibers composed of DNA, histones, and granular proteins that can entrap pathogens.^{18,19}

In ARDS, neutrophilic infiltration and NETs may lead to diffuse alveolar damage, the histopathologic hallmark of ARDS.^{18,20}

Elevated levels of IL-8 have been observed in the bronchoalveolar lavage fluid of patients with ARDS and are associated with poor clinical outcomes, including longer mechanical ventilation time, prolonged ICU stays, multiple organ failure, and increased risk of mortality.²¹⁻²³

Proposed Mechanism of Action²⁴⁻³¹

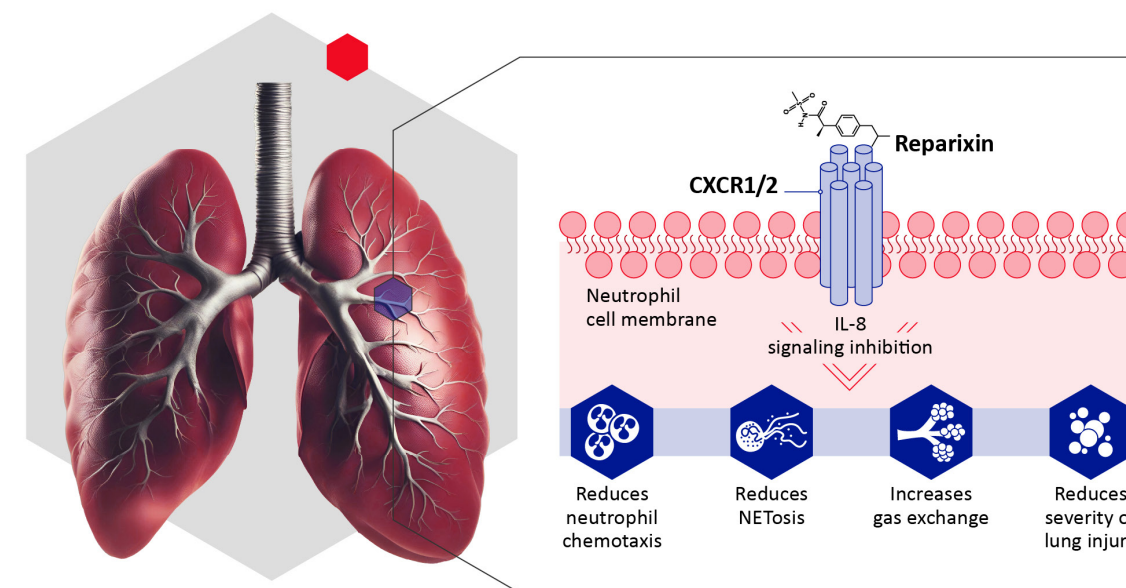


Figure 1. Reparixin is an investigational agent and may affect outcomes as proposed in the figure through inhibition of IL-8.

Data from preclinical and randomized clinical trials have shown that targeting CXCR1/CXCR2 may provide a potential therapy for ARDS, specifically by modulating or inhibiting IL-8 activity and reducing neutrophil-mediated immunopathology.^{17,32}












Reparixin is an investigational, oral, noncompetitive allosteric inhibitor of the IL-8 receptors CXCR1 and CXCR2 (Figure 1) that may reduce the damaging effects of IL-8 associated with inflammatory disorders.^{24,25} In vitro and preclinical small-animal studies have shown that binding of reparixin to CXCR1/CXCR2 can prevent leukocyte recruitment and activation of inflammation.^{24,25}

During the phase 2 REPAVID-19 trial, patients with severe COVID-19 pneumonia who received reparixin exhibited a lower rate of clinical events, including need for supplemental oxygen, need for ventilation, admission to ICU, or use of rescue medication, than did those who received standard of care.³³ Patients with severe COVID-19 in a phase 3 trial showed less progression to more invasive treatment than did those who received standard of care.³⁴ Reparixin has been well tolerated in previous clinical trials of patients with breast cancer and COVID-19 pneumonia,³³⁻³⁵ with gastrointestinal discomfort being the most widely reported side effect.³⁵

RESPIRATIO TRIAL INFORMATION

RESPIRATIO, a phase 2, multinational, multicenter, randomized, double-blind, placebo-controlled trial (NCT05496868), is underway to evaluate the efficacy and safety of oral reparixin in ameliorating lung injury and systematic inflammation in adults hospitalized with moderate-to-severe ARDS.³⁶

Key eligibility criteria

-  Men and women aged ≥18 years
-  Not currently receiving extracorporeal membrane oxygenation or high-frequency oscillatory ventilation
-  Mechanically ventilated with PaO₂/FiO₂ ratio ≤200 mmHg (in the presence of positive end-expiratory pressure ≥5 mmHg)
-  Not anticipating extubation within 24 hours of enrollment
-  Respiratory failure not fully explained by cardiac failure or fluid overload
-  No active bleeding (excluding menses) or bleeding diathesis including patients on chronically high doses of NSAIDs
-  Within 48 hours from fulfilling ARDS diagnosis (plus 12 hours if the patient is transferred from another institution)
-  No documented allergy/hypersensitivity to sulfonamides, ibuprofen, and other COX-1 and -2 inhibitors and to the study product and/or its excipients
-  Lack of chronic renal dysfunction (<30 mL/min/1.73 m² eGFR) or on renal replacement therapy
-  Not pregnant or planning to become pregnant within 30 days after the study ends
-  Lack of chronic hepatic disease: AST/ALT ≥3× ULN + total bilirubin >2× ULN or AST/ALT ≥5× ULN; Child-Pugh Score ≥7

ALT, alanine aminotransferase; AST, aspartate aminotransferase; COX, cyclooxygenase; eGFR, estimated glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drug; ULN, upper limit of normal.

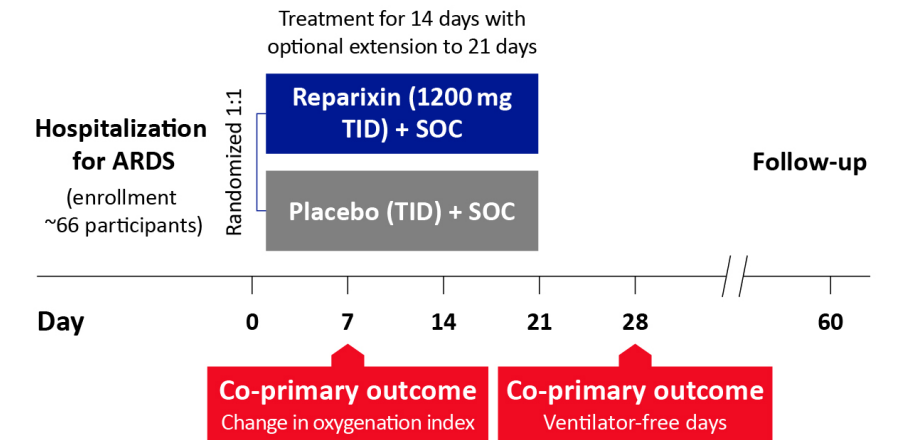
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Study Design

RESPIRATIO Study in ARDS

Phase 2, multinational, randomized, double-blind trial is ongoing to evaluate the efficacy and safety of oral reparixin as add-on therapy to SOC in moderate-to-severe ARDS



Primary endpoints

- Change in oxygenation index at Day 7^a
- Ventilator-free days at Day 28

Key secondary endpoints

- Acute lung injury score^b
- Ventilatory ratio^c
- Sequential organ failure assessment score
- Incidence of extracorporeal membrane oxygenation
- ICU-free and hospital-free days
- All-cause mortality
- Use of vasoactive medications

Safety endpoint

- Incidence of treatment-emergent adverse events and serious adverse events, biochemistry changes, ECG analysis, and incidence of secondary infections

Pharmacokinetic endpoint

- Plasma levels of reparixin and relevant metabolites

PaO₂/FiO₂, partial pressure of arterial oxygen to fraction of inspired oxygen ratio; SOC, standard of care; TID, three times a day. ^aOxygenation index is defined as percent mean airway pressure × PaO₂/FiO₂. ^bComposite of PaO₂/FiO₂ ratio, positive end-expiratory pressure, lung compliance (plateau airway pressure minus positive end-expiratory pressure/tidal volume), and extent of pulmonary infiltrates. ^cDefined as the product of minute ventilation and PaCO₂.

Visit [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT05496868) for more information.

Contact usmedinfo@dompe.com for questions or information related to clinical trial sites.

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