References

1. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307(23):2526-2533. **2.** Han S, Mallampalli RK. The acute respiratory distress syndrome: from mechanism to translation. *J Immunol.* 2015;194(3):855-860. **3.** Matthay MA, Zemans RL. The acute respiratory distress syndrome: pathogenesis and treatment. *Annu Rev Pathol.* 2011;6:147-163. **4.** Matthay MA, Arabi YM, Siegel ER, et al. Phenotypes and personalized medicine in the acute respiratory distress syndrome. *Intensive Care Med*. 2020;46(12):2136-2152. **5.** Saguil A, Fargo M. Acute respiratory distress syndrome: diagnosis and management. *Am Fam Physician*. 2012;85(4):352-358. **6.** Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1334-1349. **7.** Thompson BT, Chambers RC, Liu KD. Acute Respiratory Distress Syndrome. *N Engl J Med*. 2017;377(6):562-572**. 8.** Chen X, Tang J, Shuai W, Meng J, Feng J, Han Z. Macrophage polarization and its role in the pathogenesis of acute lung injury/acute respiratory distress syndrome. *Inflamm Res.* 2020;69(9):883-895. **9.** Neethi Raj P, Shaji BV, Haritha VH, Anie Y. Neutrophil secretion modulates neutrophil and monocyte functions during hyperglucose and/or hyperinsulin conditions in vitro. *J Cell Immunother.* 2018;4(2):65-70. **10.** Matthay MA, Zemans RL, Zimmerman GA, et al. Acute respiratory distress syndrome. *Nat Rev Dis Primers*. 2019;5(1):18. **11.** Pham T, Rubenfeld GD. Fifty years of research in ARDS. The epidemiology of acute respiratory distress syndrome. A 50th birthday review. *Am J Respir Crit Care Med*. 2017;195(7):860-870. **12.** Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir Med*. 2014;2(8):611-620. **13.** Calfee CS, Delucchi KL, Sinha P, et al. ARDS subphenotypes and differential response to simvastatin: secondary analysis of a randomized controlled trial. *Lancet Respir Med*. 2018;6:691. **14.** Ochiai R. Mechanical ventilation of acute respiratory distress syndrome. *J Intensive Care*. 2015;3(1):25. **15.** Menk M, Estenssoro E, Sahetya SK, et al. Current and evolving standards of care for patients with ARDS. *Intensive Care Med*. 2020;46(12):2157-2167. **16.** Ha H, Debnath B, Neamati N. Role of the CXCL8-CXCR1/2 axis in cancer and inflammatory diseases. *Theranostics*. 2017;7(6):1543-1588. **17.** Cesta MC, Zippoli M, Marsiglia C, et al. The role of interleukin-8 in lung inflammation and injury: implications for the management of COVID-19 and hyperinflammatory acute respiratory distress syndrome. *Front Pharmacol*. 2021;12:808797. **18.** Bendib I, de Chaisemartin L, Granger V, et al. Neutrophil extracellular traps are elevated in patients with pneumonia-related acute respiratory distress syndrome. *Anesthesiology*. 2019;130(4):581-591. **19.** Brinkmann V, Reichard U, Goosmann C, et al. Neutrophil extracellular traps kill bacteria. *Science*. 2004;303(5663):1532-1535. **20.** Yang SC, Tsai YF, Pan YL, Hwang TL. Understanding the role of neutrophils in acute respiratory distress syndrome. *Biomed J*. 2021;44(4):439-446. **21.** Parsons PE, Eisner MD, Thompson BT, et al. Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. *Crit Care Med.* 2005;33(1):1-6; discussion 230-232. **22.** Hildebrand F, Stuhrmann M, van Griensven M, et al. Association of IL-8-251A/T polymorphism with incidence of acute respiratory distress syndrome (ARDS) and IL-8 synthesis after multiple trauma. *Cytokine*. 2007;37(3):192-199. **23.** Cartin-Ceba R, Hubmayr RD, Qin R, et al. Predictive value of plasma biomarkers for mortality and organ failure development in patients with acute respiratory distress syndrome. *J Crit Care*. 2015;30(1):219.e1-7. **24.** Williams AE, Chambers RC. The mercurial nature of neutrophils: still an enigma in ARDS? *Am J Physiol Lung Cell Mol Physiol*. 2014;306(3):L217-230. **25.** Bertini R, Allegretti M, Bizzarri C, et al. Noncompetitive allosteric inhibitors of the inflammatory chemokine receptors CXCR1 and CXCR2: prevention of reperfusion injury. *Proc Natl Acad Sci U S A.* 2004;101(32):11791-11796. **26.** Zarbock A, Allegretti M, Ley K. Therapeutic inhibition of CXCR2 by reparixin attenuates acute lung injury in mice. *Br J Pharmacol*. 2008;155(3):357-364. **27.** Landoni G, Piemonti L, Monforte AdA, et al. A multicenter phase 2 randomized controlled study on the efficacy and safety of reparixin in the treatment of hospitalized patients with COVID-19 pneumonia. *Infect Dis Ther*. 2022;11(4):1559-1574. **28.** Landoni G, Voza A, Puoti M, et al. A phase 3 study to evaluate the efficacy and safety of reparixin in severe COVID-19 pneumonia. European Respiratory Society International Congress; September 4-6, 2022; Barcelona, Spain. **29.** Goldstein LJ, Perez RP, Yardley D, et al. A window-of-opportunity trial of the CXCR1/2 inhibitor reparixin in operable HER-2-negative breast cancer. *Breast Cancer Res.* 2020;22(1):4. **30.** (U.S.) NLoM. Add-on Reparixin in Adult Patients With ARDS. https://clinicaltrials.gov/ct2/show/NCT05496868?term=NCT05496868&draw=2&rank=1. Accessed August 18, 2022.

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TARGETING INFLAMMATION FOR ACUTE RESPIRATORY DISTRESS SYNDROME

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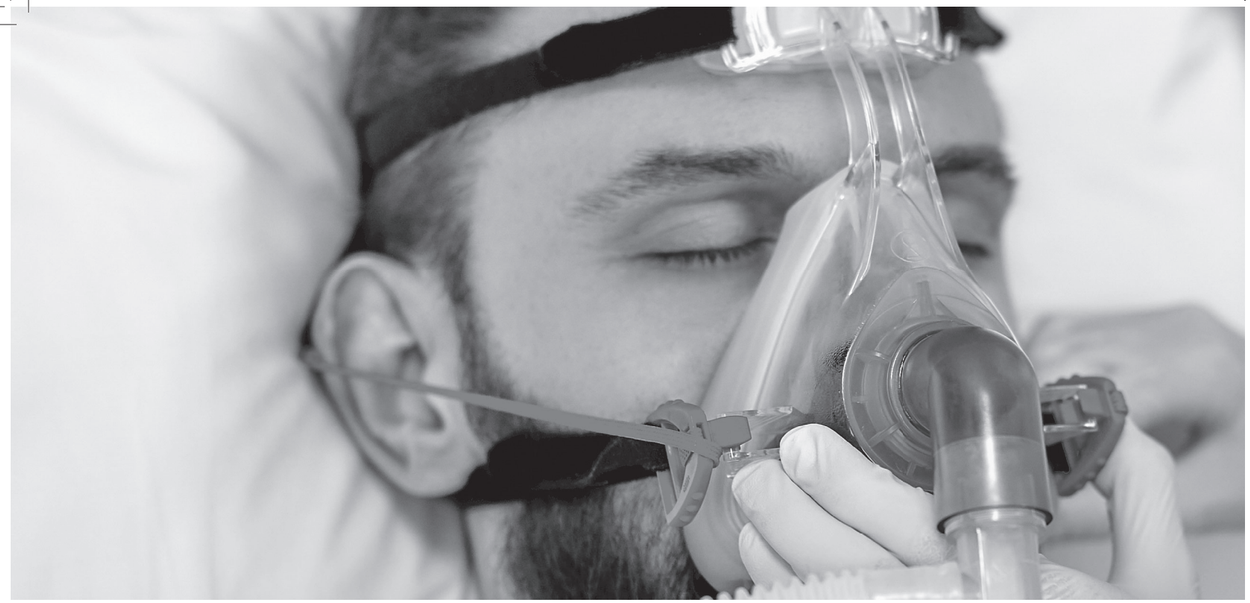

ARDS BACKGROUND

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 (PaO_2/FiO_2 of 201-300 mmHg), moderate (PaO_2/FiO_2 of 101-200 mmHg), or severe (PaO_2/FiO_2 ≤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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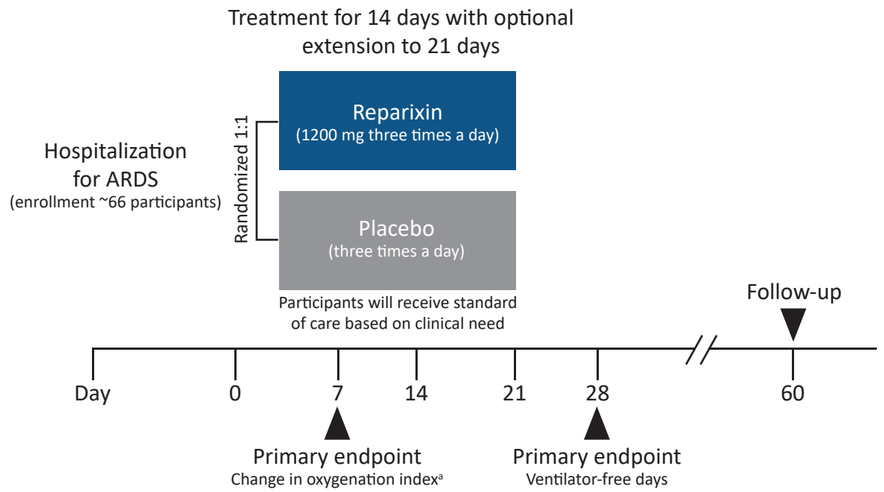
Study Design



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

PaO_2/FiO_2, partial pressure of arterial oxygen to fraction of inspired oxygen ratio. [a]Oxygenation index is defined as percent mean airway pressure × PaO_2/FiO_2. [b]Composite of PaO_2/FiO_2 ratio, positive end-expiratory pressure, lung compliance (plateau airway pressure minus positive end-expiratory pressure/tidal volume), and extent of pulmonary infiltrates. [c]Defined as the product of minute ventilation and $PaCO_2$.

Visit ClinicalTrials.gov (NCT05496868) for more information.

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

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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.[30]

Key eligibility criteria

- Men and women aged ≥18 years
- Mechanically ventilated with PaO_2/FiO_2 ratio ≤200 mmHg (in the presence of positive end-expiratory pressure ≥5 mmHg)
- Respiratory failure not fully explained by cardiac failure or fluid overload
- Hospitalized within previous 7 days and fulfilled ARDS criteria within previous 48 hours
- No severe renal dysfunction
- No significant chronic liver disease
- No active malignancy, active bleeding, or gastrointestinal dysmotility
- Not currently receiving extracorporeal membrane oxygenation or high-frequency oscillatory ventilation
- Not anticipating extubation within 24 hours of enrollment
- No history of gastrointestinal bleeding or perforation due to previous nonsteroidal anti-inflammatory drug or recurrent peptic ulcer/hemorrhage
- No previous known allergy to ibuprofen or medications belonging to the sulfonamide class
- Not pregnant or planning to become pregnant within 30 days after the study ends

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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]

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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]

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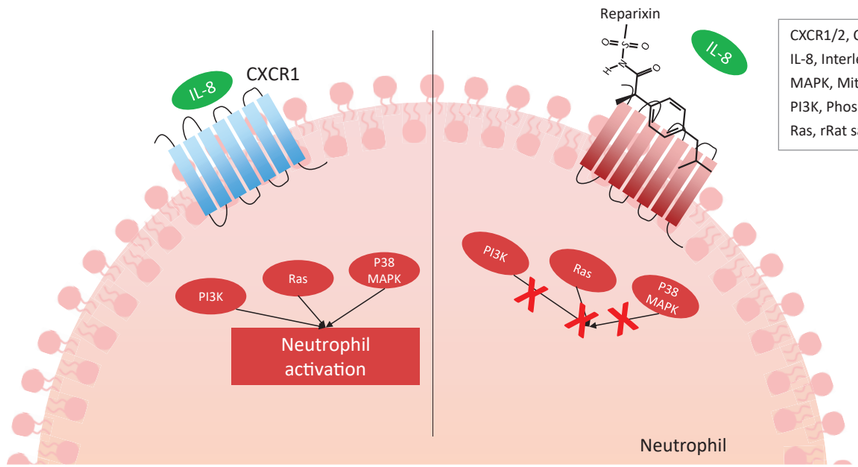
Reparixin binds to CXCR1/2 and may reduce excessive hyperinflammation



CXCR1/2, CXC chemokine receptors 1 and 2
IL-8, Interleukin 8
MAPK, Mitogen-activated protein kinase
PI3K, Phosphatidylinositol 3-kinase
Ras, rRat sarcoma virus protein

Figure 1. Reparixin binds to IL-8 receptors CXCR1 and CXCR2, and it can inhibit inflammatory pathways and subsequent leukocyte activation, which may prevent hyperinflammation.

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.[17,24]

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.[25,26] In vitro and preclinical small-animal studies have shown that binding of reparixin to CXCR1/CXCR2 can prevent leukocyte recruitment and activation of inflammation.[25,26]

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.[27] 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.[28] Reparixin has been well tolerated in previous clinical trials of patients with breast cancer and COVID-19 pneumonia,[27-29] with gastrointestinal discomfort being the most widely reported side effect.[29]

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