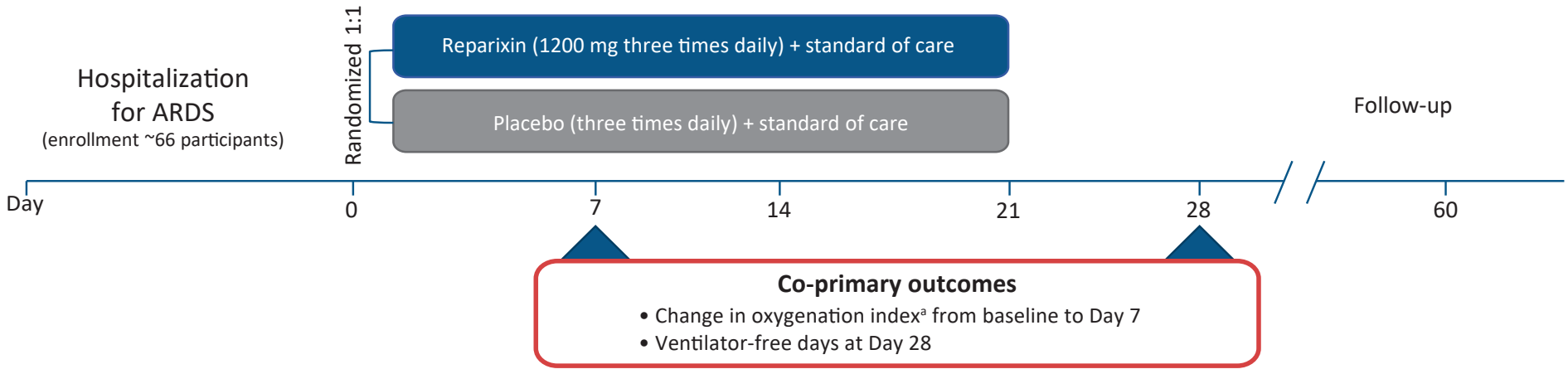
RESPIRATIO IS NOW ENROLLING AT YOUR HOSPITAL

ATTENTION: Are you caring for patients hospitalized with acute respiratory distress syndrome (ARDS)?

A phase 2, multinational, randomized, double-blind, placebo-controlled trial (NCT05496868)[1] is ongoing at your hospital to evaluate the efficacy and safety of reparixin as an add-on therapy to the standard of care for adults hospitalized with moderate-to-severe ARDS



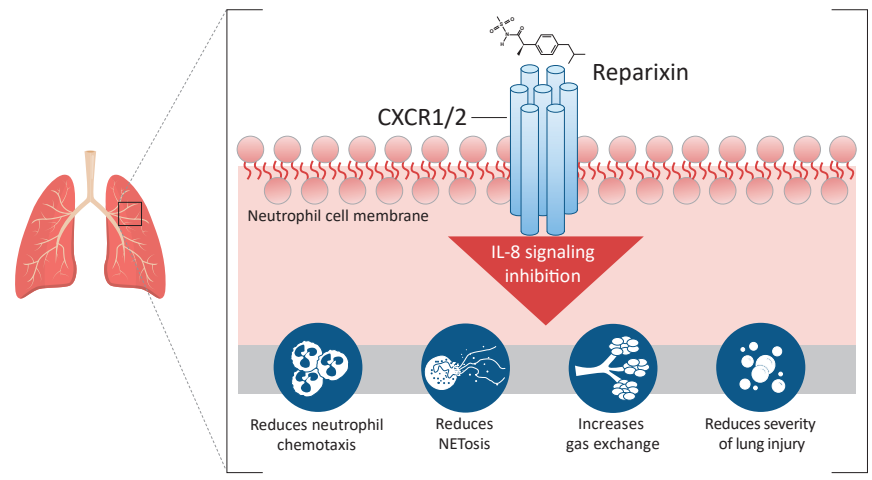
TARGET PATIENT POPULATION

- Hospitalized adults (aged ≥18 years)
- Mechanically ventilated (invasive) patients with PaO_2/FiO_2 ratio ≤200 mmHg in the presence of PEEP ≥5 cm H_2O
- Respiratory failure not fully explained by cardiac failure or fluid overload
- Hospitalized within previous 7 days and fulfills ARDS criteria within previous 48 hours
- Not pregnant or planning to become pregnant
- No known hypersensitivity to ibuprofen or medications belonging to the sulfonamide class
- Lack of renal or hepatic dysfunction/history of moderate-severe chronic hepatic disease
  - Renal dysfunction: <30 mL/min/1.73 m^2 eGFR or end-stage renal disease with renal replacement therapy
  - Hepatic dysfunction: AST/ALT ≥3× ULN + total bilirubin >2× ULN or AST/ALT ≥5× ULN; Child-Pugh class B or C
- No active malignancy, active bleeding, or gastrointestinal dysmotility

INVESTIGATIONAL AGENT: REPARIXIN

- Reparixin is an investigational, potent, noncompetitive allosteric inhibitor of the interleukin-8 receptors CXCR1 and CXCR2[2]
- Reducing interleukin-8 signaling may attenuate inflammatory responses by reducing neutrophil recruitment to the lung (**Figure**)[3]
- Modulation of interleukin-8 activity via blockade of its receptors may reduce progression of ARDS[4,5]

Proposed Mechanism of Action[2,3,6-11]



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

To learn more about the clinical trial, enrollment, and principal investigator at your site, visit **www.clinicaltrials.gov/study/NCT05496868** or contact **usmedinfo@dompe.com** for additional information on how you can get involved in clinical research at your site!

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CXCR, chemokine receptor; eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; FiO_2, fraction of inspired oxygen; IL, interleukin; NET, neutrophil extracellular trap; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; ULN, upper limit of normal. [a]Change in percentage of mean airway pressure × FiO_2/PaO_2.
1. ClinicalTrials.gov. https://www.clinicaltrials.gov/study/NCT05496868. Accessed September 7, 2023. **2.** Bertini et al. *Proc Natl Acad Sci U S A*. 2004;101:11791-11796. **3.** Zarbock et al. *Br J Pharmacol*. 2008;155:357-364. **4.** Williams and Chambers. *Am J Physiol Lung Cell Mol Physiol*. 2014;306:L217-L230. **5.** Ha et al. *Theranostics*. 2017;7:1543-1588. **6.** Alsabani et al. *Br J Anaesth*. 2022;128:283-293. **7.** Hosoki et al. *Clin Exp Allergy*. 2019;49:130-132. **8.** Russo et al. *Am J Respir Cell Mol Biol*. 2009;40:410-421. **9.** Schraufstatter et al. *Am J Physiol Lung Cell Mol Physiol*. 2001;280:L1094-L1103. **10.** Song et al. *Respir Res*. 2022;23:155. **11.** Boro et al. *J Immunol*. 2017;199:1660-1671.

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

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