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TARGETING INFLAMMATION FOR COMMUNITY-ACQUIRED PNEUMONIA

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COMMUNITY-ACQUIRED PNEUMONIA BACKGROUND

Community-acquired pneumonia (CAP) is an infection of the lower respiratory tract, or organs that help you breathe, caused by bacterial or viral pathogens.[1]

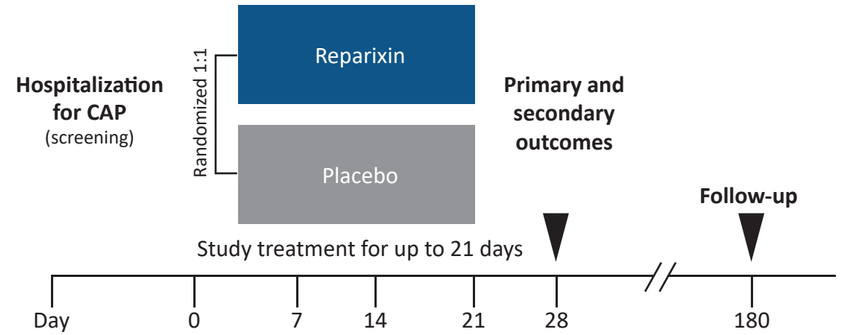
Patients with CAP may present with fever, chills, and/or respiratory symptoms, including shortness of breath, chest pain, and cough.[2] Elderly patients may present without a fever, and pre-existing lung conditions may complicate diagnosis.[3] Chest imaging, such as an x-ray, is critical to confirm symptom-based diagnoses and will show white or dense areas, indicating inflammation in the lung.[1]

As microorganisms, such as bacteria, build up in the lung, the immune system is activated to aid in clearing and fighting the infection. Immune cells release inflammatory mediators, or cytokines, to recruit additional cell types and initiate mechanisms to eliminate the microorganism.[4-6]

Certain cytokines, including interleukin (IL) 8, are highly elevated in patients with CAP.[7] Elevated IL-8 levels are associated with severe CAP, poor clinical outcomes, and death.[8,9]

Increased IL-8 levels drive recruitment of white blood cells called neutrophils to the lung, which can lead to the formation of neutrophil extracellular traps (NETs).[10] NETs are composed of DNA and protein complexes that trap and kill microorganisms.[11] However, an excess of NETs can promote tissue injury, including in the lungs.[10] Excess NETs play an important role in the development of severe CAP and associated complications, cardiovascular events (events related to the heart), and sepsis (over-active immune response to infection).[10-12] These conditions may lead to difficulty breathing or complications that require hospitalization or admission to the intensive care unit.[10,12]

Study Design



Two 600-mg tablets of reparixin or placebo, administered orally 3 times a day. Participants will receive standard of care based on clinical need

Primary endpoint

- Proportion of participants experiencing death or requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) by Day 28

Key secondary endpoints

- Participants recovered and discharged at Day 28
- Ventilator-free days at Day 28
- Need for invasive mechanical ventilation or ECMO at Day 28
- Length of hospital stay
- All-cause mortality at Day 180

Safety and pharmacokinetic assessments

Visit ClinicalTrials.gov (NCT05254990) for more information.

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

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REPAVID-22 TRIAL INFORMATION

REPAVID-22 (NCT05254990), a phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial, is underway to evaluate the efficacy and safety of oral reparixin in limiting disease progression in adults hospitalized with CAP.

Key eligibility criteria

- Men and women aged ≥18 years
- Hospitalized for clinically suspected CAP, defined as the occurrence of the following:
  - ≥1 of the following signs/symptoms: dyspnea, cough, purulent sputum, crackles (rales), or rhonchi
  - Body temperature >38°C or <36°C (before or during admission) or leukocytosis (>local upper limit of normal)
  - New/Increased pulmonary infiltrate(s) by chest imaging
- Need for noninvasive supplemental oxygen
  - SpO_2 <92% at room air (or PaO_2/FiO_2 <300 mmHg)
- <72 hours from hospital admission
- Hepatic function: Alanine aminotransferase (ALT) or aspartate transaminase (AST) <5× upper limit of normal (ULN)
- Renal function: >50 mL/min/1.73 m^2 estimated glomerular filtration rate (eGFR)
- No need for invasive mechanical ventilation or ECMO
- No active bleeding, previous intracranial hemorrhage, or recurrent peptic ulcer/ gastrointestinal hemorrhage
- No previous hypersensitivity to ibuprofen or medications belonging to the sulfonamide class
- Not pregnant or planning to become pregnant within 30 days of end of the study
- No use of >2 immunosuppressive medications, immunosuppression status, or solid organ or bone marrow transplant
- No complex CAP-associated conditions (eg, fungal pulmonary infection, abscess, empyema, significant bilateral pleural effusion, pulmonary embolism)

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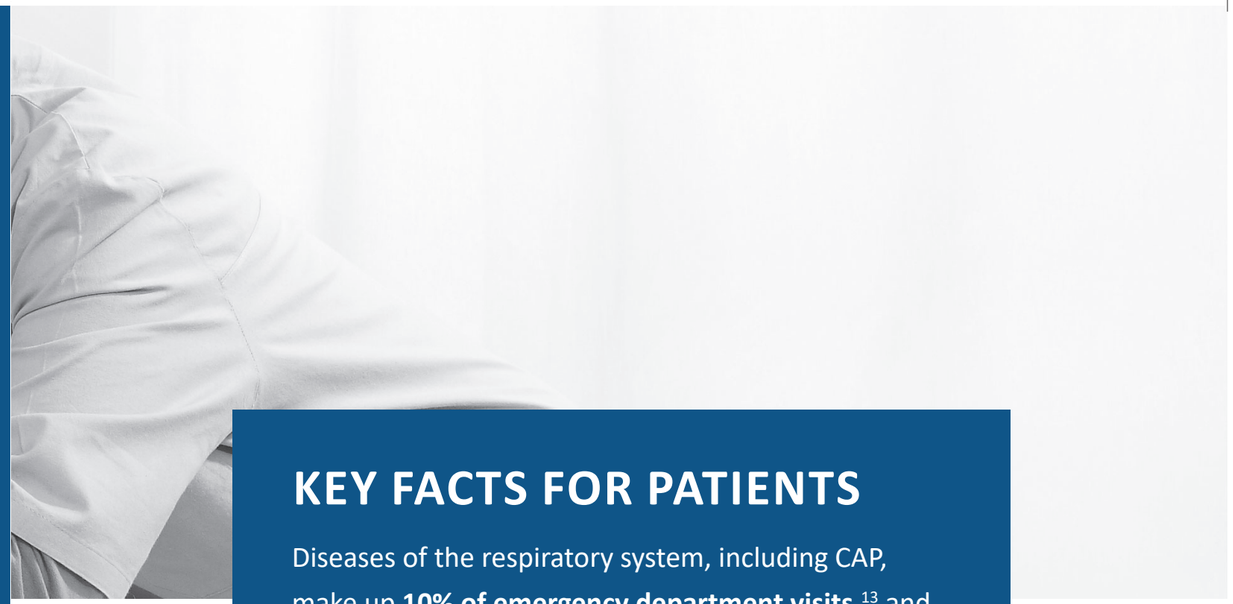

KEY FACTS FOR PATIENTS

Diseases of the respiratory system, including CAP, make up **10% of emergency department visits,**[13] and **nearly 6% of patients with CAP are admitted to the intensive care unit.**[14]

According to the World Health Organization, lower respiratory infections, including CAP, are the most common infectious cause of death worldwide.[15]

Factors that increase the risk of adults to be diagnosed with CAP include increased age, certain disease states, smoking, environmental exposures, poor nutrition, and medications that may decrease immune system function (such as corticosteroids).[1,16]

Currently, the **standard of care** for patients hospitalized with CAP focuses on **treating the infective cause** with standard antimicrobial therapy.[17,18]

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DOMPÉ IS EXPLORING IF INHIBITION OF IL-8 SIGNALING CAN LIMIT DISEASE PROGRESSION AND DEATH ASSOCIATED WITH CAP

IL-8 (also known as CXCL8) is a cytokine associated with high inflammation potential in the immune system during severe lung inflammation and infection.[19]

IL-8 is an important factor that attracts neutrophils to the lung; binding of IL-8 to its cellular receptors, CXCR1 and CXCR2, leads to recruitment and activation of neutrophils and release of NETs to initiate inflammation, potentially leading to tissue injury during CAP.[10,19,20]

Dysregulated neutrophil activity and elevated levels of IL-8 are associated with disease severity, poor outcomes, and an increased risk of death.[8,9,12] Reducing IL-8 activity by blockade of CXCR1/CXCR2 may reduce neutrophil activity and associated tissue damage seen in CAP.[10]

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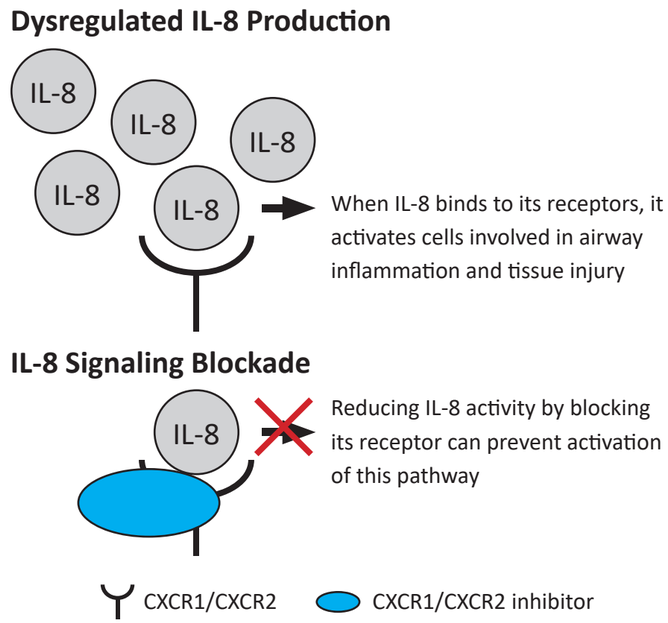

Reparixin is an investigational drug that is being assessed for its ability to reduce the IL-8 signaling pathway in patients with CAP

Reparixin is an investigational, oral, noncompetitive allosteric inhibitor of the IL-8 receptors CXCR1 and CXCR2 and may reduce the damaging effects of IL-8 associated with inflammatory disorders.[21] In vitro and preclinical animal studies have shown that binding of reparixin to CXCR1/CXCR2 can prevent white blood cell recruitment and activation of inflammation.[21,22]

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 intensive care unit, or use of rescue medication, than did those who received standard of care.[23] 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.[23] Reparixin has been well tolerated in previous clinical trials of patients with breast cancer and COVID-19 pneumonia,[23-25] with gastrointestinal discomfort being the most widely reported side effect.[25]

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