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Reducing the Burden and Improving QoL in Non-Cystic Fibrosis Bronchiectasis:

New Insights into the Pathophysiology and Treatment

Provided by RMEI Medical Education, LLC

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This activity is supported by an educational grant from Insmed.

Recognizing the Burden of Bronchiectasis

Molly Mailes, MSN, RN, MEDSURG-BC

Disease Burden

US Prevalence

- 340,000 to 520,000

Demographics

- Caucasians
- Females
- Never smokers
- Mean age: 64 ± 14 years
- Prior NTM disease

Severity Associated with:

- Poor nutrition/low BMI
- *P. aeruginosa* infection

Characterized by:

- Dilated bronchi
- Poor mucus clearance
- Repeated bacterial infection
- Bronchial wall injury

Patient Burden

- Reduced QoL
- Significant financial burden
- Significant morbidity
- Increased mortality with low BMI
- Osteopenia/osteoporosis

Despotes KA, et al. *Chronic Obstr Pulm Dis.* 2020;7(4):390-403; Choate R, et al. *Respir Med.* 2020;177:106285; Diehl N, Johnson MM. *South Med J*. 2016;109(12):779-783.

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Mortality Risk

- 1.15 times greater mortality versus matched controls
- Mortality greatest in elderly patients and men
- Comorbidities increasing mortality:
  - Asthma
  - COPD
  - Pneumonia
  - Lung cancer
  - Cardiovascular disease

Choi H, et al. *Sci Rep.* 2021;11(1):7126.

Diagnosing Bronchiectasis

Margaret Johnson, MD

Recognizing Bronchiectasis

Clinical Suspicion

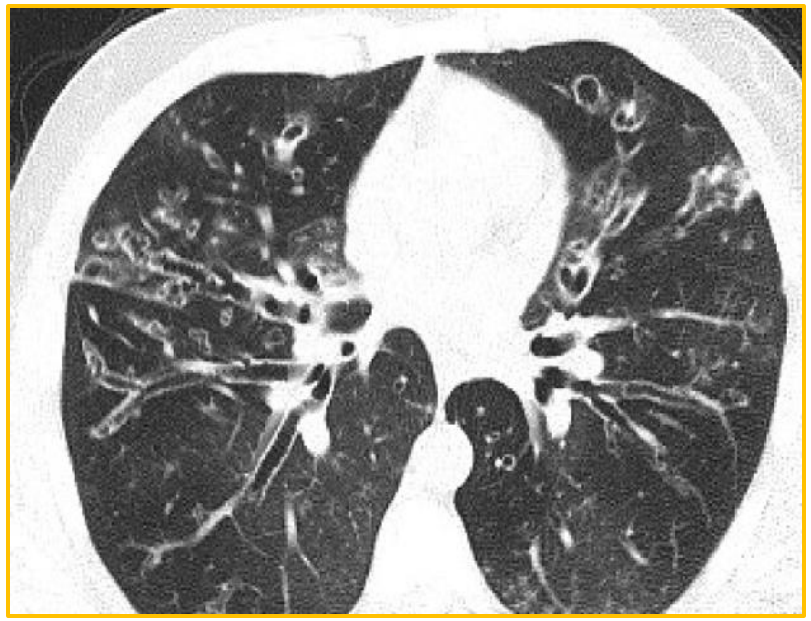
- Cough
- Excessive sputum production
- Recurrent respiratory infections
- Pleuritic chest pain
- Hemoptysis
- Breathlessness
- Lethargy
- Weight loss/low BMI
- *P. aeruginosa* or NTM in the respiratory tract

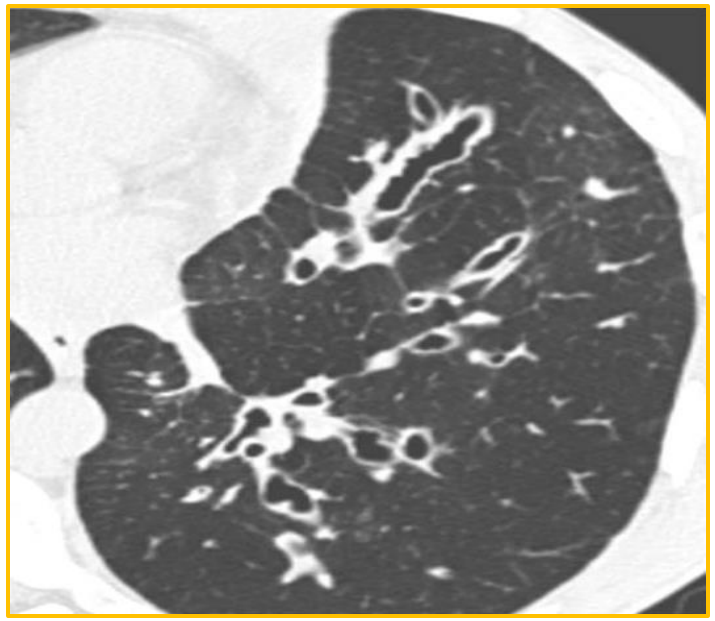
At-Risk Population

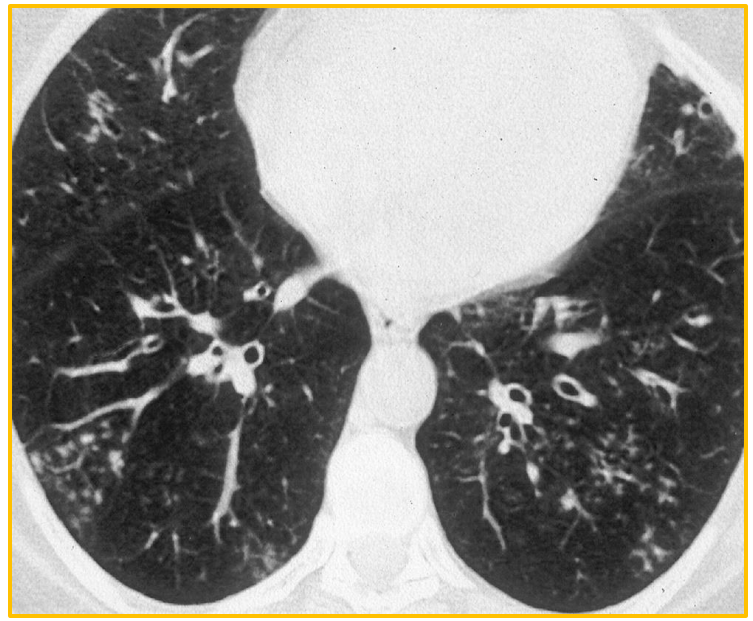
- Older age
- Female gender
- Co-existent lung disease
- Prior infections
- Autoimmune disease
- Immunodeficiency
- Chronic aspiration

Quinn TM, Hill TA. *Clin Interv Aging.* 2018;13:1649-1656; Macfarlane L, et al. *Clin Med* (Lond). 2021;21(6):e571-e577.

CT Signs of Bronchiectasis







- Airway dilation
- Mucus plugging
- Lack of airway tapering
- Tree-in-bud opacities

Images Courtesy of M. Johnson.

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Clinically Significant Bronchiectasis?

CT

- Airway diameter > blood vessel
- Lack of airway tapering
- Visibility of airway in periphery

Symptoms

(At least 2 of following)

- Cough most days of the week
- Sputum production most days of the week
- History of exacerbations

International Consensus Recommendations for Diagnosis

Aliberti S, et al. *Lancet Respir Med.* 2022;10(3):298-306.

Diagnostic Testing for Bronchiectasis

Labs

- CBC with differential
- History directed lab work-up:
  - RF, anti-CCP, ANCA, A1AT, HIV-1 serology
- Respiratory Cultures
  - Bacteria
  - Fungus
  - AFB
- Antibody Testing
  - Serum total IgE
  - Aspergillus fumigatus IgE
  - Serum IgG, IgA, IgM
  - Baseline antibodies against capsular polysaccharides of S. pneumoniae
    - Vaccinate if low and reassess titer at 4 to 8 weeks

Additional Testing (Selected)

- Cystic fibrosis
- Primary ciliary dyskinesia
- Reflux and aspiration
- Bronchoscopy to rule out endobronchial lesion or foreign body

Idiopathic Cases

- About 40% of bronchiectasis cases are idiopathic

Hill AT, et al. *Thorax.* 2019;74(Suppl 1):1-69.

Bronchiectasis Pathophysiology and Emerging Therapies

Mark Metersky, MD

Current Treatment Options

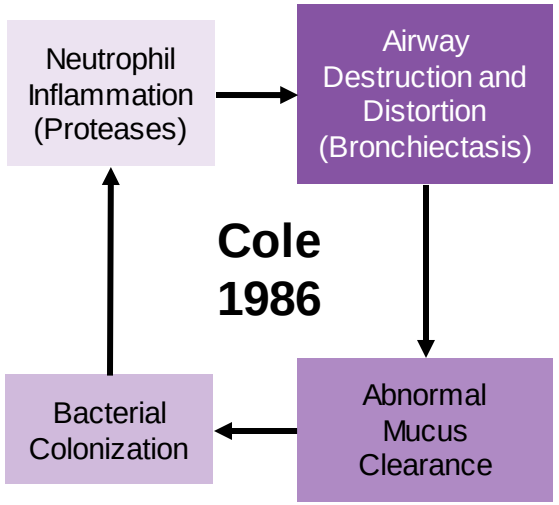
- Airway clearance devices and chest physical therapy
- Hypertonic saline
- Bronchodilators
- Anti-inflammatory treatment
  - Chronic low-dose macrolide therapy
  - Inhaled corticosteroids
- Antimicrobial therapy (oral, inhaled)
- Surgery and transplant (limited role)

Role of the Nurse or Respiratory Therapist

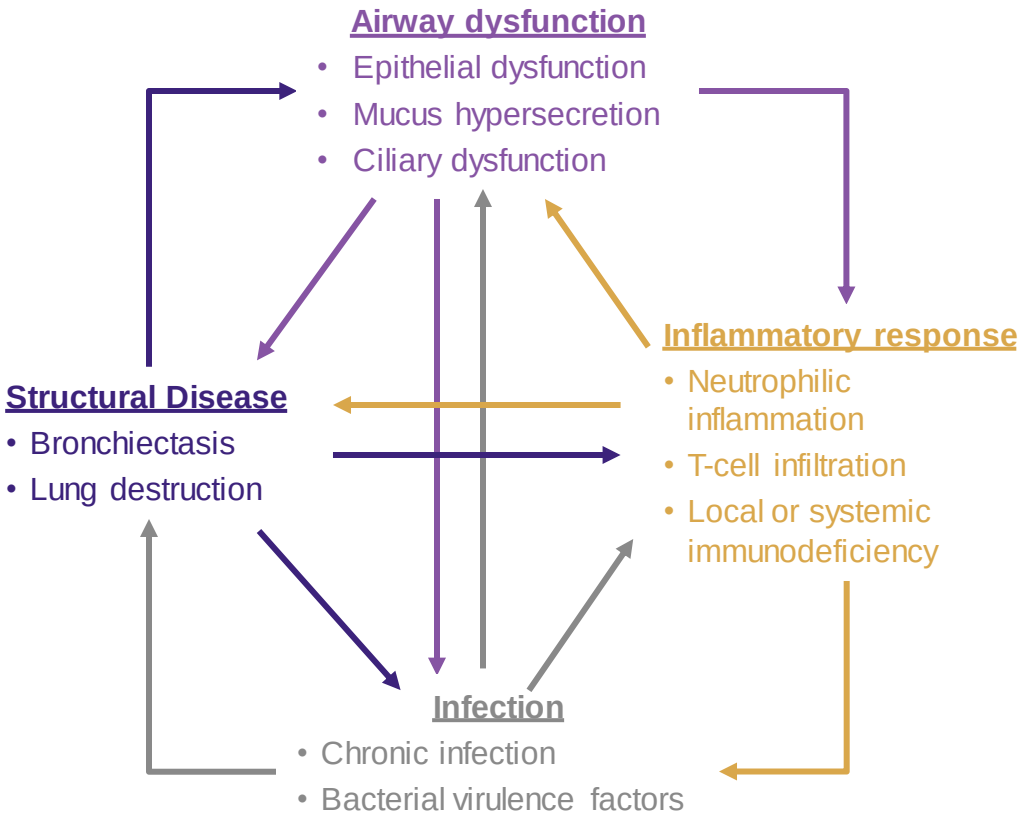
- Educate on airway clearance therapy
  - What it is
  - Why it is important and consequences of mucus accumulation
  - Proper use and cleaning of mucus-clearing devices
  - Integrating treatment into their daily regimen
- Discuss fears and misconceptions

Bronchiectasis: Pathogenesis

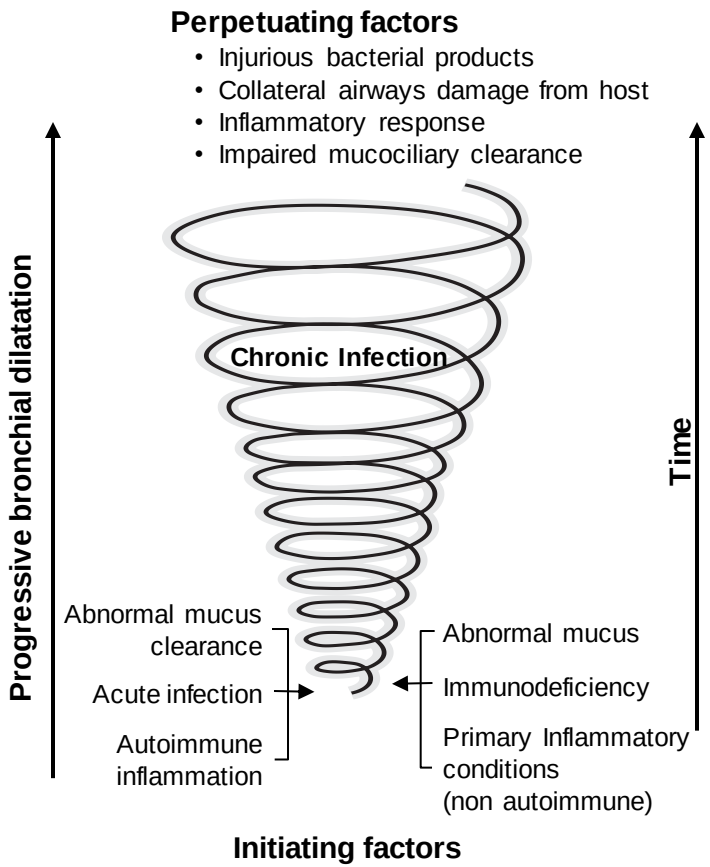
Vicious Cycle[1]



Vicious Vortex[2]



Alternative Vicious Vortex[3]



1. McShane PJ, et al. *Am J Respir Crit Care Med.* 2013;188(6):647-656.
2. Flume PA, et al. *Lancet.* 2018;392(10150):880-890.
3. Metersky M, Barker AF. *Clin Chest Med.* 2022;43(1):35-46.

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Role of Neutrophils

Sputum Neutrophils are Associated with:

- Decline in pulmonary function
- Bacterial colonization
- Severe disease
- Inflammatory morbidity

Neutrophil Elastase is an NSP Associated with:

- Extracellular matrix degradation
- Mucus gland hyperplasia
- Increased mucus production
- Reduced ciliary beating rate
- Direct epithelial damage

Inhibiting DPP-1

- DPP-1 activates neutrophil elastase in the bone marrow during neutrophil maturation
- Direct neutrophil elastase inhibition failed to improve NCFBE in Phase 2 studies
- DPP-1 is currently an investigational target

DPP-1, dipeptidyl peptidase 1

Usansky H, et al. *Clin Pharmacol Drug Dev.* 2022;11(7):832-842..

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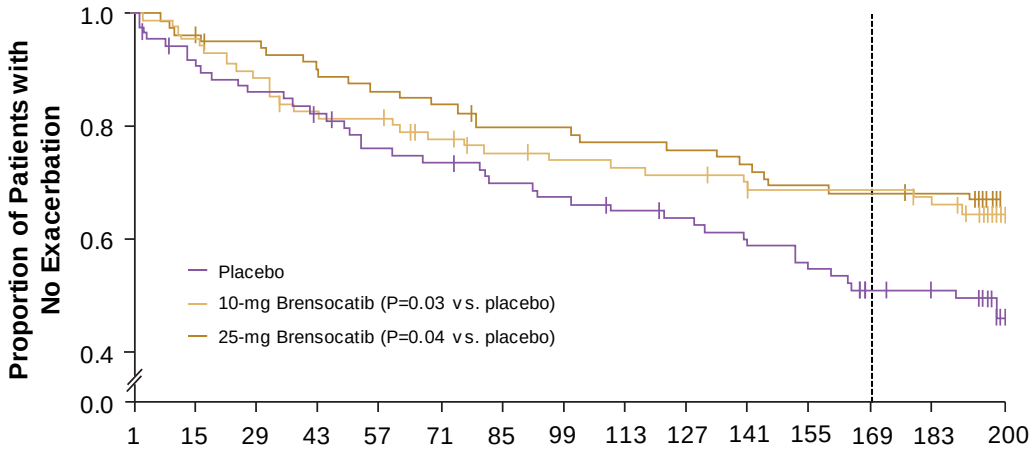
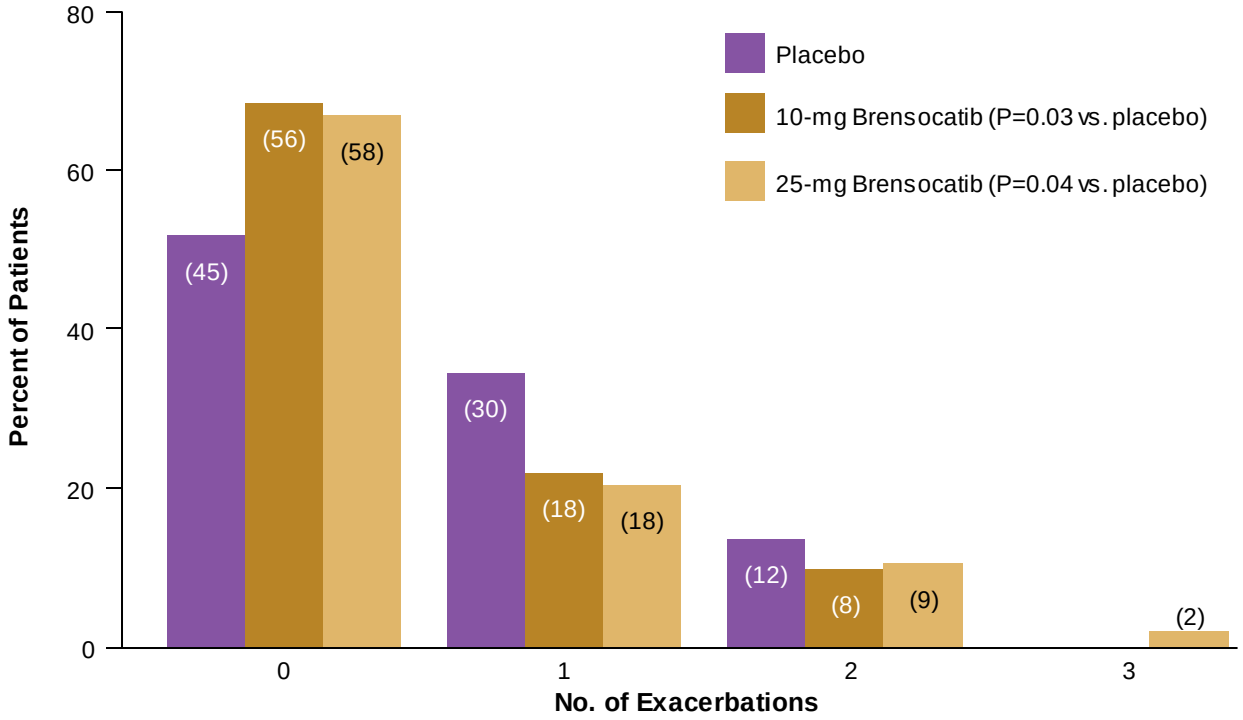
Brensocatib: Phase 2 WILLOW

Mechanism of Action

- Selective reversible DPP-1 inhibitor
- Oral small molecule
- Blocks NSP activation



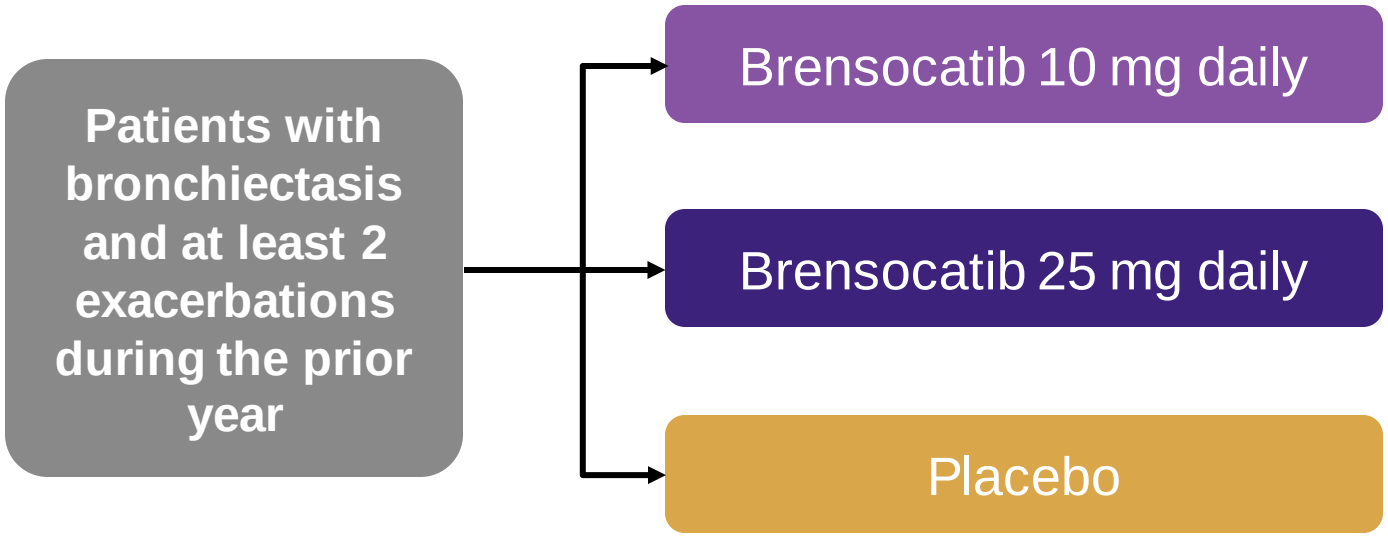


Click here to view the clinicaltrials.gov study record for this study: https://tinyurl.com/4w4a8wa4

NSP, neutrophil serine protease

Chalmers JD, et al. *N Engl J Med*. 2020;383(22):2127-2137.

Brensocatib: Phase 3 ASPEN[1]



- **Primary outcome:**
  Pulmonary exacerbations
- **Secondary outcomes**:
  - QoL
  - Lung function
  - Tolerability

Click here to view the clinicaltrials.gov study record for this study: https://tinyurl.com/yeyv45va

Eligible patients completing the ASPEN study were invited to participate in the expanded access trial:[2] https://tinyurl.com/2d67tana

1. ClinicalTrials.gov: NCT04594369.
2. ClinicalTrials.gov: NCT05344508.

Role of Eosinophils

Inflammatory Response[1,2]

Up to a **third** of patients with bronchiectasis have a predominant eosinophilic rather than neutrophilic inflammatory response

IL-5 Receptor (IL-5R)

Expressed on the surface of eosinophils

Is there a role for anti-IL5 or anti-eosinophilic therapy?

Anti-IL5 monoclonal antibodies directly bind the alpha subunit of the IL-5R leading to apoptosis of eosinophils

1. Rademacher J, et al. *Eur Respir J.* 2020;55(1):1901333.
2. Guan WJ, et al. *J Allergy Clin Immunol Pract*. 2022;S2213-2198(22)01129-1.
3. ClinicalTrials.gov: NCT05006573. For study record, click here: https://tinyurl.com/yae7dbv6 .

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Other Agents in Development

Phase 1

- Neutrophil elastase inhibitor BI 1323495[1]
- Neutrophil elastase inhibitor CHF 6333[2] (Inhaled)
- Nebulized human plasma-derived polyvalent immunoglobulin G (IgG): CSL787[3]

Phase 2

- DPP-1 inhibitor HSK31858[4]
- Ascorbic acid/glutathione/bicarbonate inhalation[5]

For these and other ongoing clinical trials for NCFBE, please see: https://tinyurl.com/ye9f3w43

1. ClinicalTrials.gov: NCT04656275.
2. ClinicalTrials.gov: NCT04010799.
3. ClinicalTrials.gov: NCT04643587.
4. ClinicalTrials.gov: NCT05601778.
5. ClinicalTrials.gov: NCT05495243.

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