Multimodular Curriculum-Based Learning for CME

Neutrophil-Based Targeting in Non-Cystic Fibrosis Bronchiectasis (NCFBE)

CME

*Focus on Patients with **Recurrent Exacerbations** Despite Standard Therapies*

PROGRAM CHAIR
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Clinical Case Study

CASE

58-year-old female

Medical history	• Bronchiectasis • Recurrent exacerbator despite standard therapies
Profile	• Long-term macrolide therapy • Inhaled antibiotics with ≥4 exacerbations/year.
Management	• Nonpharmacologic Therapy • Pharmacologic Therapy

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Nonpharmacologic Therapy

CASE

- **Airway Clearance**
  - Regular exercise
  - Vibratory PEP
  - Chest percussion
  - Nebulized hypertonic saline
  - Chest wall oscillation
  - Autogenic drainage
  - Active cycle of breathing
- **Pulmonary rehabilitation**
- **Nutrition**
- **GERD**
  - Lifestyle modifications

Best choice is what the patient will do
- Education
- Time commitment

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Traditional Pharmacologic Therapy for Bronchiectasis

CASE

- Mucolytic therapy
  - 7% hypertonic saline
- Anti-inflammatory (immune modulating) therapy
  - Macrolide
- Inhaled antipseudomonal Therapy

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Bronchiectasis Exacerbation

CASE

- According to international expert consensus (Hill et al.), an **exacerbation** is diagnosed when a patient experiences a deterioration in **three or more** of the following key symptoms for 48 hours or longer:
  - Cough
  - Sputum volume and/or consistency
  - Sputum purulence (color change to yellow/green or thicker mucus)
  - Breathlessness and/or reduced exercise tolerance
  - Fatigue and/or malaise
  - Hemoptysis (coughing up blood)
- **AND** a clinician determines that a change in bronchiectasis treatment (such as starting antibiotics) is necessary.

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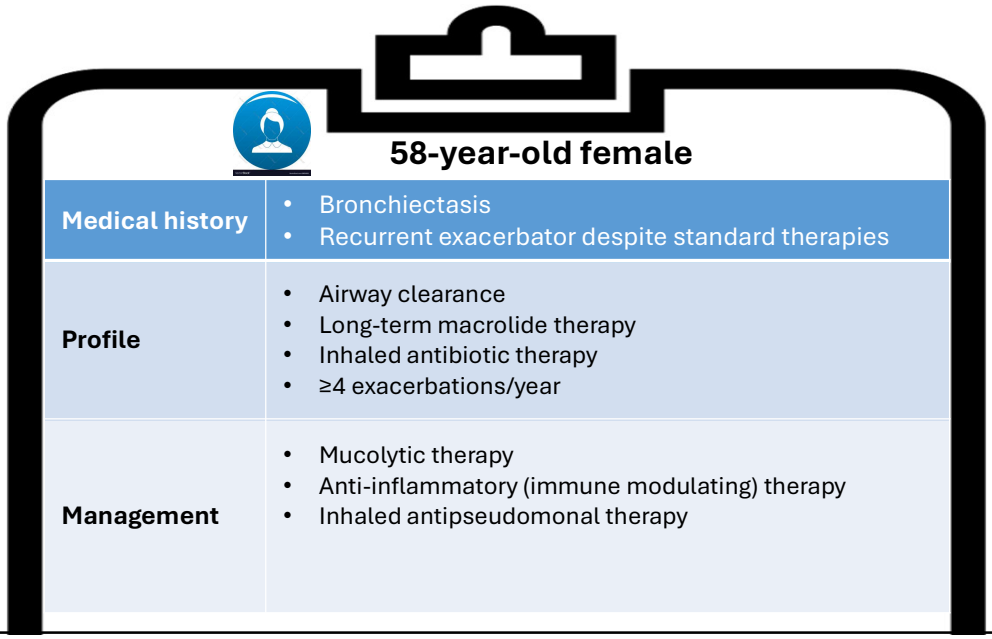
What's Wrong With This Picture?

CASE



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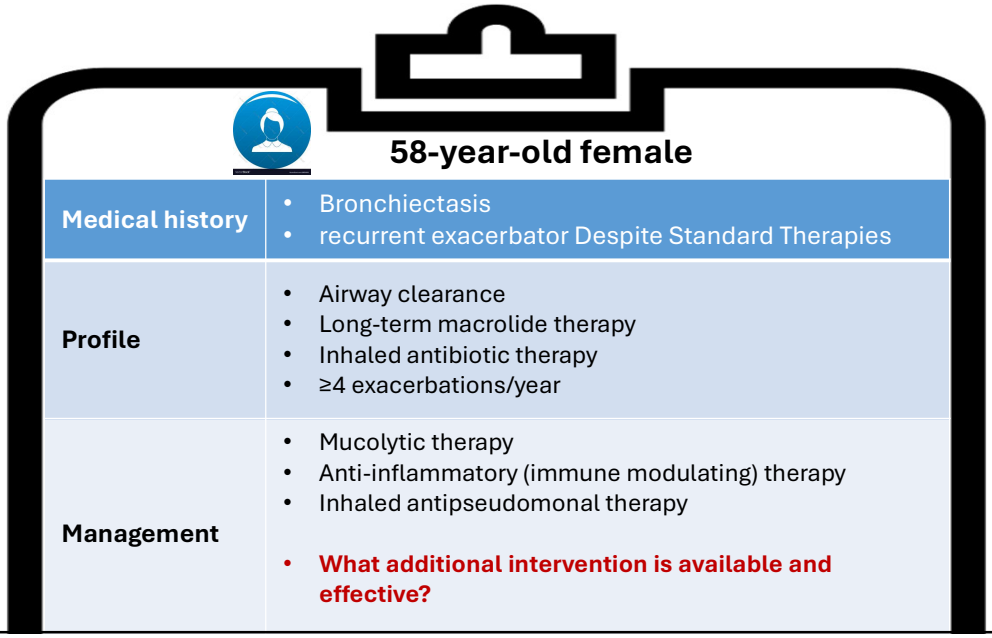

58-year-old female

Medical history	• Bronchiectasis • recurrent exacerbator Despite Standard Therapies
Profile	• Airway clearance • Long-term macrolide therapy • Inhaled antibiotic therapy • ≥4 exacerbations/year
Management	• Mucolytic therapy • Anti-inflammatory (immune modulating) therapy • Inhaled antipseudomonal therapy • **What additional intervention is available and effective?**

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Brensocatib

- Bronchiectasis is a disease characterized by chronic, self-perpetuating bronchial inflammation.
- Brensocatib is an anti-inflammatory drug but not a steroid or related to familiar over-the-counter anti-inflammatory drugs such as ibuprofen.
- Brensocatib has no direct effect on the lung

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Brensocatib

- Brensocatib blocks the activity of the enzyme dipeptidyl peptidase 1, also known as cathepsin C.
- By inhibiting DPP1, brensocatib prevents the activation of neutrophil serine proteases (NSPs) like neutrophil elastase and proteinase 3, which are overactive in inflammatory lung diseases such as bronchiectasis.
- Brensocatib effects maturing polymorphonuclear (PMN) cells in the bone marrow so that they release lower levels of NSPs at sites of inflammation such as bronchiectasis.
- In bronchiectasis they result is less intense inflammation in the bronchial tube and less potent recruitment of other PMNs that would augment the inflammatory response.

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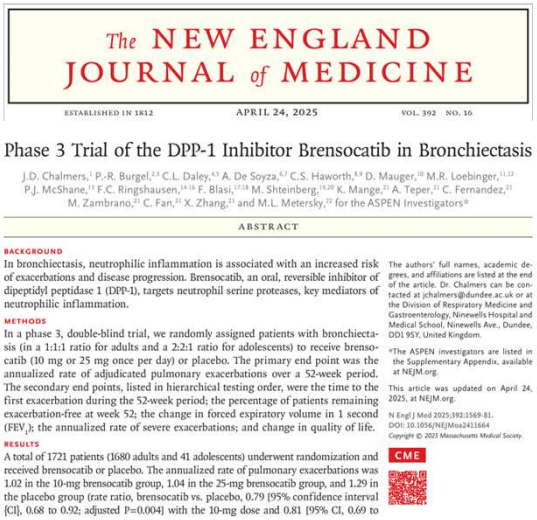
Phase 3 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis



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Phase 3 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis

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ABSTRACT

BACKGROUND

In bronchiectasis, neutrophilic inflammation is associated with an increased risk of exacerbations and disease progression. Brensocatib, an oral, reversible inhibitor of dipeptidyl peptidase 1 (DPP-1), targets neutrophil serine proteases, key mediators of neutrophilic inflammation.

METHODS

In a phase 3, double-blind trial, we randomly assigned patients with bronchiectasis (in a 1:1:1 ratio for adults and a 2:2:1 ratio for adolescents) to receive brensocatib (10 mg or 25 mg once per day) or placebo. The primary end point was the annualized rate of adjudicated pulmonary exacerbations over a 52-week period. The secondary end points, listed in hierarchical testing order, were the time to the first exacerbation during the 52-week period; the percentage of patients remaining exacerbation-free at week 52; the change in forced expiratory volume in 1 second (FEV_1); the annualized rate of severe exacerbations; and change in quality of life.

RESULTS

A total of 1721 patients (1680 adults and 41 adolescents) underwent randomization and received brensocatib or placebo. The annualized rate of pulmonary exacerbations was 1.02 in the 10-mg brensocatib group, 1.04 in the 25-mg brensocatib group, and 1.29 in the placebo group (rate ratio, brensocatib vs. placebo, 0.79 [95% confidence interval [CI], 0.68 to 0.92; adjusted P=0.004] with the 10-mg dose and 0.81 [95% CI, 0.69 to

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*The ASPEN investigators are listed in the Supplementary Appendix, available at NEJM.org.

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CME

Chalmers JD, N Engl J Med 2025;392:1569-1581

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- The primary end point was the annualized rate of adjudicated pulmonary exacerbations over a 52-week period.
- The secondary end points were:
  - The time to the first exacerbation during the 52-week period;
  - The percentage of patients remaining exacerbation-free at week 52;
  - The change in forced expiratory volume in 1 second (FEV_1);
  - The annualized rate of severe exacerbations;
  - And change in quality of life.

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Phase 3 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis

- A total of 1721 patients (1680 adults and 41 adolescents) underwent randomization and received brensocatib or placebo.
- The rate of pulmonary exacerbations was:
  - 1.02 in the 10-mg brensocatib group, P=0.004 c/w placebo
  - 1.04 in the 25-mg brensocatib group, P=0.005 c/w placebo
  - 1.29 in the placebo group
- The time to the first exacerbation (compared to placebo) was:
  - 0.81, with the 10-mg dose P=0.02
  - 0.83 with the 25-mg dose P=0.04

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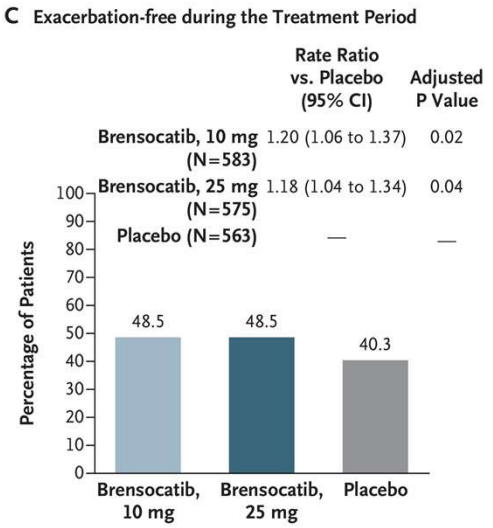
Phase 3 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis

Results

- 48.5% of patients remained exacerbation-free at week 52, as compared with 40.3% in the placebo group: P=0.02 with 10-mg dose and P=0.04 with 25-mg dose.



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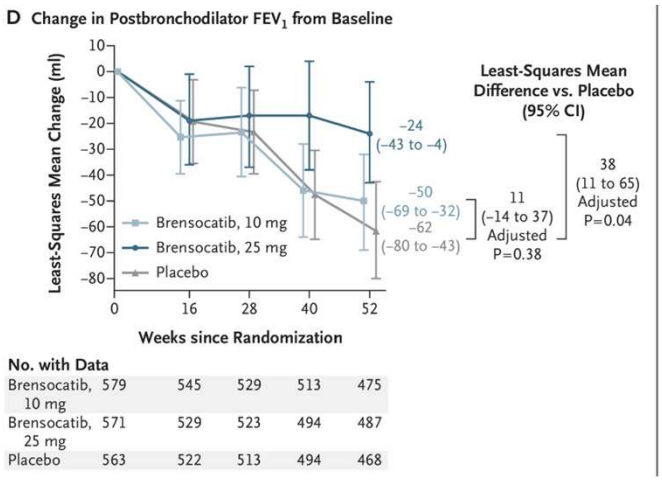
Phase 3 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis

Results

- At week 52, FEV_1 declined by 50 ml with the 10-mg dose, P=0.38 and 24 ml with the 25-mg dose, P=0.04 and 62 ml with placebo
- The incidence of adverse events was similar across groups, except for a higher incidence of hyperkeratosis with brensocatib.



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Phase 3 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis

Conclusions

- Among patients with bronchiectasis, once-daily treatment with brensocatib (10 mg or 25 mg) led to a lower annualized rate of pulmonary exacerbations than placebo, and the decline in FEV_1 was less with the 25-mg dose of brensocatib than with placebo.

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Phase 3 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis

- This pivotal study of brensocatib resulted in demonstrating to the FDA that the drug can decreases the frequency of bronchiectasis exacerbation for some patients and can be associated with maintenance of pulmonary function versus placebo in some patients.
- The 10 mg and 25 mg doses both diminish the frequency of exacerbations but only the 25 mg dose was associated with the maintenance of lung function.
- Side effects are infrequent and generally mild. They include infections in the nose and throat, headache, increase in blood pressure, skin reactions including hyperkeratosis, dental and gum issues, and allergic reactions.

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Brensocatib

- Brensocatib is the first drug approved by the Food and Drug Administration (FDA) specifically for the treatment of bronchiectasis.
- The label reads simply "for patients with noncystic fibrosis bronchiectasis".
- The FDA made no stipulations about or requirements for a certain number of bronchiectasis exacerbations within 12 months of the prescription.
- This is also the only medication known to protect pulmonary function over a 12-month period.

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Brensocatib Adverse Events: Compared with Placebo

- **General adverse events**
  - The most common adverse reactions reported included upper respiratory tract infection, headache, rash, dry skin, hyperkeratosis, and hypertension.
- **Cardiovascular:** (1% to 10%): Hypertension
- **Dermatologic:** (1% to 10%): Rash, dry skin, hyperkeratosis, alopecia
- **Gastrointestinal:** (10% or more): Periodontal adverse reactions (up to 10.1%) (1% to 10%): Gingival adverse reactions
- **Hepatic:** Increased ALT and AST, increase alkaline phosphatase
- **Nervous system:** (1% to 10%): Headache
- **Respiratory** (10% or more): Upper respiratory tract infection (up to 29%)
  - Upper respiratory tract infection included coronavirus, COVID-19, influenza, upper respiratory tract infection, viral infection, and viral upper respiratory tract infection.

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Brensocatib

- No fatal side effects
- Side effects reversible after discontinuation of the drug
- No GI symptom side effects
- No drug-drug interactions
- No medical contraindications
- Brensocatib administration does not result in immune suppression or compromise

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Brensocatib: Other Considerations

- Symptoms??
  - Addrizzo-Harris D, et al. **Brensocatib in Participants of Asian Race with Non-cystic FibrosisBronchiectasis**: A Subgroup Analysis of the ASPEN Trial. Pulm Ther. 2026, Sep;12(3):917-936.
    - Improved QOL-B RSS score, p = 0.0034 versus placebo.
  - Meterskey M et al. **Brensocatib eases daily symptom burden in bronchiectasis.** A Subgroup Analysis of the ASPEN Trial Submitted for presentation at CHEST 2026
    - Brensocatib reduced symptom burden in patients with NCFBE regardless of exacerbation frequency or severity
- Insurance coverage requirements

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Recurrent Exacerbator Despite Standard Therapies

CASE

Physician takeaway:

- Persistent exacerbations despite optimized care highlight inflammation as an independent driver of disease
- Neutrophil-modulating agents may break the infection–inflammation cycle and reduce exacerbation frequency without adding antibiotic burden.

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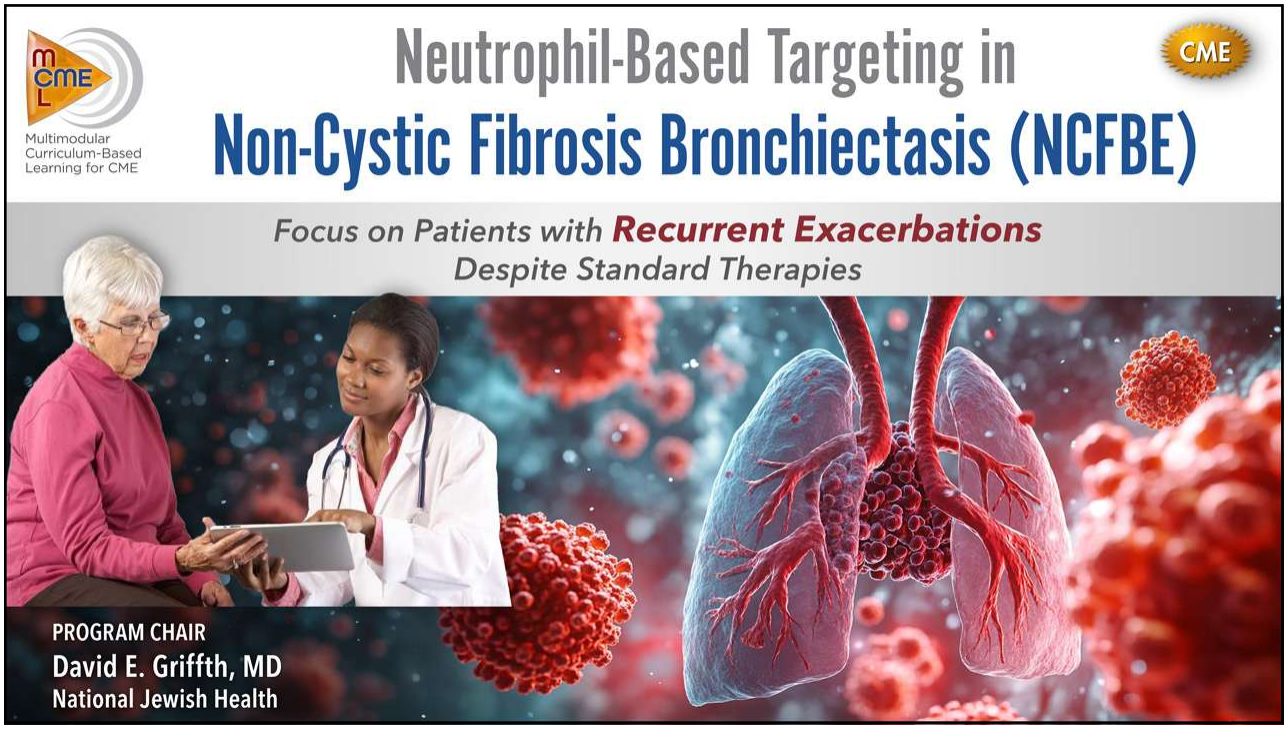

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