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REVIEW

The convergent pathway of obstructive lung disease: the disease-modifying potential of dipeptidyl peptidase 1 inhibition in COPD, asthma and bronchiectasis overlap

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Abstract

The management of chronic obstructive lung diseases, particularly severe asthma, chronic obstructive pulmonary disease (COPD) and non-cystic fibrosis bronchiectasis, is complicated by frequent overlap syndromes such as asthma–bronchiectasis overlap and bronchiectasis–COPD overlap syndrome. These overlapping phenotypes are characterized by severe symptoms, frequent exacerbations, accelerated lung function decline and increased mortality, driven by a common, destructive endotype: persistent, neutrophil-dominant airway inflammation. This inflammation is fuelled by the overactivity of neutrophil serine proteases, notably neutrophil elastase, which drives the self-perpetuating 'vicious vortex' of structural damage and infection. Traditional therapies, including inhaled corticosteroids and type 2 (T2) inflammation-targeted biologics, are often ineffective against this non-T2, neutrophilic inflammation. Brensocatib, a first-in-class, oral, reversible inhibitor of dipeptidyl peptidase 1 (DPP1), offers a novel, targeted strategy. By inhibiting DPP1 — the master activator of neutrophil serine proteases in the bone marrow — brensocatib effectively 'disarms' neutrophils before they reach the lungs. The phase III ASPEN trial in non-cystic fibrosis bronchiectasis demonstrated its disease-modifying potential, showing a significant reduction in the annualized rate of exacerbations and, critically, a statistically significant slowing of the decline in forced expiratory volume in 1 second in the 25 mg arm (a benefit not observed with the 10 mg dose). Subgroup analysis confirmed consistent efficacy in the high-risk bronchiectasis–COPD overlap syndrome population. These findings validate DPP1 inhibition as a first potential disease-modifying therapy. This strategy is poised to fundamentally shift clinical focus from symptom control to the preservation of lung function for patients with severe, neutrophilic-driven neutrophilic overlap syndromes.

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Keywords: asthma, asthma–bronchiectasis overlap, bronchiectasis–COPD overlap, chronic obstructive pulmonary disease, dipeptidyl peptidase 1 inhibitor, non-cystic fibrosis bronchiectasis.

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Introduction

Chronic obstructive lung diseases, historically siloed into distinct categories of asthma and chronic obstructive pulmonary disease (COPD), are increasingly recognized as overlapping syndromes. A critical, and often under-diagnosed, third party in this convergence is non-cystic fibrosis bronchiectasis (NCFBE). Asthma–bronchiectasis overlap (ABO) and COPD–bronchiectasis overlap, also known as bronchiectasis–COPD overlap syndrome (BCOS), create severe clinical phenotypes characterized by high prevalence and symptom burden, frequent exacerbations, and accelerated lung

function decline.[1,2] This severity is largely driven by a shared endotype: persistent, neutrophil-dominant airway inflammation. Traditional therapies offer symptomatic relief but fail to interrupt this cycle.[3] Several phase II studies and currently one phase III study have confirmed that dipeptidyl peptidase 1 (DPP1) inhibitors reduce neutrophil serine protease (NSP) activity in the airways and have clinical benefits in bronchiectasis, including primarily a reduction in exacerbations and improvement in other clinical endpoints such as quality of life and slowing the decline in lung function. DPP1 inhibition may also be a promising therapeutic avenue in other diseases involving neutrophil inflammation such as chronic obstructive respiratory diseases.[4]

Brensocatib, a first-in-class reversible DPP1 inhibitor that can be administered orally, represents a paradigm shift in this regard. By inhibiting DPP1 in the bone marrow, brensocatib blocks the maturation of NSPs within neutrophils, effectively 'disarming' them before they reach the lungs. Landmark trials, including the phase III ASPEN study, have demonstrated the ability of brensocatib to significantly reduce annualized exacerbation rate (AER) and, critically, slow the decline in forced expiratory volume in 1 second (FEV_1) in patients with bronchiectasis, including those with BCOS.[5] This review synthesizes the pathophysiology and key aspects of these overlap syndromes and analyses the clinical evidence for brensocatib as the first potential disease-modifying therapy for this neutrophilic endotype designed to break the cycle.

Methods

Data sources and study selection

This review synthesizes the current medical literature concerning the convergent pathway of obstructive lung diseases, specifically severe asthma, COPD and NCFBE, and the potential of DPP1 inhibition as a disease-modifying strategy. The methodology involved a comprehensive analysis of the existing medical literature using PubMed, Ovid, Scopus, Embase and Cochrane Library databases up to 27 November 2025, to detail the pathophysiology of neutrophil-dominant airway inflammation, the limitations of traditional therapies in overlap syndromes, and the clinical evidence supporting the use of the first-in-class, oral, reversible DPP1 inhibitor brensocatib. The search strategy included the specific research terms: "COPD", "asthma", "NCFBE", "DPP1", "NE", "NSPs", "vicious vortex", "exacerbation", "inflammation", "lung function decline", "infections", "quality of life" AND "safety".

Data sources and focus

The review focused on synthesizing information regarding the definition and severe clinical consequences of overlap syndromes, primarily ABO and BCOS; the mechanism driven by NSPs, notably neutrophil elastase (NE), which is the common, destructive endotype of these conditions; the mechanism of action of brensocatib as an 'upstream' inhibitor of DPP1 in the bone marrow, which leads to the production of 'disarmed' neutrophils; and key clinical trial data on brensocatib in NCFBE.

Analysis of clinical evidence

A detailed analysis of clinical trials was performed, with a particular focus on phase II and phase III trials.

Overlap subgroup analysis

Specific attention was paid to subgroup analyses from the phase III trial, particularly for the BCOS population, to assess the consistency of efficacy and the signal for slowing FEV_1 decline in this high-risk phenotype.

Safety and tolerability

The safety profile was assessed, including the rate of serious adverse events (SAEs), pneumonia and on-target cutaneous/oral effects.

Review

The clinical challenge of convergent airway disease

For decades, the diagnosis of chronic airway disease has relied on a simplified paradigm: traditionally, asthma was defined as a reversible allergic and/or eosinophilic condition, whilst COPD as an irreversible, neutrophilic condition related to smoking. This dichotomy, whilst useful, is clinically incomplete. In reality, a vast 'grey zone' exists, in which patients exhibit features of both conditions — a phenotype now recognized as asthma–COPD overlap (ACO) as well as often with activation of multiple inflammatory pathways (Table 1).[6]

However, this two dimensional overlap misses a crucial third axis of structural lung damage: bronchiectasis. Defined by the permanent, abnormal dilation of the bronchi, bronchiectasis is not merely a rare disease but a common comorbidity that dramatically worsens outcomes.

Prevalence of bronchiectasis overlap

The prevalence of bronchiectasis in patient populations with obstructive disease is alarmingly high. Depending on the cohort and imaging sensitivity (high-resolution computed tomography (HRCT)), bronchiectasis is identified in 25–40% of patients with severe asthma (ABO) and in 30% to over 50% of patients with moderate-to-severe COPD (BCOS).[7–9] BCOS is characterized by

Table 1. Key characteristics of asthma, COPD and bronchiectasis overlap syndromes.

Feature	ABO	BCOS
Primary disease	Severe, often difficult-to-treat asthma	Moderate-to-severe COPD
Underlying aetiology	Allergic/T2 inflammation (often transitioning to non-T2), chronic infection	Smoking, environmental toxins, chronic infection
Inflammatory endotype	Predominantly neutrophilic (often T2-low), mixed eosinophilic/neutrophilic	Predominantly neutrophilic
Blood and exhaled biomarkers	BEC, FeNO, AATD, fibrinogen, procalcitonin	BEC, FeNO, AATD, fibrinogen, procalcitonin
Sputum characteristics	Often purulent, high neutrophil count, elevated active NE	Chronic purulent sputum, high neutrophil count, elevated active NE
Exacerbation frequency	High, severe	Very high, severe
Bacterial colonization	Common, *Pseudomonas aeruginosa* frequent	Very common, *Pseudomonas aeruginosa* frequent
Lung function decline	Accelerated compared to asthma alone	Significantly accelerated compared to COPD alone
Treatment challenges	Poor response to ICS/T2 biologics, frequent antibiotic use	High risk of pneumonia with ICS, frequent antibiotic use

AATD, alpha-1 antitrypsin deficiency; ABO, asthma–bronchiectasis overlap; BCOS, bronchiectasis–COPD overlap syndrome; BEC, blood eosinophil count; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; NE, neutrophil elastase; T2, type 2.

symptoms common to both bronchitis and COPD, including a persistent, productive cough, poor exercise tolerance and reduced lung capacity, often leading to frequent flare-ups. The condition is caused by a mix of factors such as genetics, infections, smoking and environmental pollutants. Diagnosis requires a comprehensive evaluation, typically involving pulmonary function tests, imaging and blood eosinophil count to detect the underlying inflammation. Patients with BCOS also face a higher risk of serious cardiovascular issues, including heart disease and stroke.[10]

The clinical consequence of bronchiectasis overlap

These overlapping phenotypes are not academic classifications; they represent the most severe and difficult-to-treat cases in respiratory medicine. Patients with ABO or BCOS experience significantly higher rates of hospital admission, more frequent and severe exacerbations, increased chronic sputum production and bacterial colonization (especially *Pseudomonas aeruginosa*), poorer quality of life, accelerated decline in lung function (FEV_1) and increased all-cause mortality.[7–10]

The central challenge in treating these patients is that the inflammation is often non-type 2 (T2) (non-eosinophilic) and instead driven by a relentless neutrophilic inflammation, rendering many cornerstone therapies, such as inhaled corticosteroids (ICS) and T2-targeted biologics, far less effective. From a purely speculative point of view, it could be hypothesized (with caution) that reducing systemic inflammation (through the deactivation of neutrophils) could theoretically reduce cardiovascular risk in patients with COPD. It is well known that chronic systemic inflammation in COPD is an important cardiovascular risk factor.[11]

The pathophysiological nexus: a 'vicious vortex' fuelled by neutrophils

The link between asthma, COPD and bronchiectasis is a self-perpetuating cycle of damage often called the 'vicious vortex', a concept first proposed by Cole in 1986 and revised many years later by Flume et al.[12,13] In overlap syndromes, this cycle is amplified by pre-existing conditions as follows: (1) the insult and impaired clearance: in COPD, the initial insult is cigarette smoke or other toxins, which damages cilia and sparks inflammation. In asthma, chronic T2 inflammation or allergic stimuli can lead to mucus plugging and airway remodelling. In both, this creates a state of impaired mucociliary clearance. (2) Bacterial colonization: stagnant mucus becomes a nutrient-rich reservoir for bacteria. Pathogens like *Haemophilus influenzae* and, more ominously, *P. aeruginosa* establish chronic infections and form biofilms. (3) The

neutrophil influx: the immune system responds to this persistent bacterial load by recruiting a massive influx of neutrophils into the airways. (4) The neutrophil's arsenal — NSP release: in the fight against the bacteria, neutrophils degranulate, releasing a highly toxic payload of NSPs from their azurophilic granules. (5) Collateral damage and cycle progression: this is the critical step. NSPs are indiscriminate — whilst they attack bacteria, they also devastate host tissue.

A deeper look at NSP release

The destructive capacity of NSPs is the engine of bronchiectasis and the link between the overlap conditions.[14,15] NE is the primary culprit as one of the most destructive enzymes in the human body. NE induces structural damage as it directly degrades elastin, the key protein responsible for the elastic recoil of the airway walls. This enzymatic destruction leads to the irreversible bronchial dilation that defines bronchiectasis. NE is a potent secretagogue, which leads to mucus hypersecretion. It cleaves membrane-tethered mucins (like MUC5AC and MUC5B) from goblet cells, leading to the characteristic chronic, purulent sputum that further impairs clearance.[16] Subsequently, NE directly damages ciliated epithelial cells, slowing or stopping the ciliary beat, thus worsening the root problem of impaired clearance. Finally, NE leads to impaired immunity as it can cleave and degrade antibodies (IgG) and other immune proteins, crippling the local immune response.

Whilst less studied than NE, proteinase 3 (PR3) is also highly destructive. It degrades extracellular matrix components and, significantly, cleaves and activates pro-inflammatory cytokines like pro-IL-1β, amplifying the inflammatory cascade.[17] Cathepsin G (CatG) is a powerful pro-inflammatory agent, acting as a potent mucus secretagogue and degrading proteoglycans in the airway matrix.[18] Azurocidin 1 (AZU1), also known as heparin-binding protein or CAP37, is an antimicrobial glycoprotein found in the secretory and azurophilic granules of neutrophils.[19] AZU1 is homologous to NE but lacks protease activity due to differences in two amino acids. It is released immediately in response to infection and is one of the components of neutrophil extracellular traps. A recent study has hypothesized a new potential mechanism through which AZU1 drives disease pathogenesis in bronchiectasis, demonstrating the elimination of AZU1 from the airways via DPP1 inhibition.[20]

NSP release leads to the cycle of impaired clearance → infection → neutrophil influx → NSP release → structural damage and further impaired clearance.[12,13] Asthma and COPD act as accelerators, either by initiating the clearance impairment (smoking-induced ciliary damage in COPD) or by contributing to the inflammatory burden (asthma's switch to a neutrophilic phenotype, often driven by the infections themselves).[21]

The therapeutic gap: why existing therapies fail in neutrophilic overlap

The management of ABO and BCOS is notoriously difficult because standard therapies are misaligned with the underlying neutrophilic endotype.

Inhaled corticosteroids

As the backbone of asthma control and eosinophilic COPD, ICS are highly effective at suppressing eosinophilic (T2) inflammation. However, their efficacy in neutrophil-dominant inflammation is poor. Furthermore, in COPD, high-dose ICS is associated with an increased risk of pneumonia — a serious event in a patient already colonized with bacteria and suffering from bronchiectasis.[22]

T2-targeted biologics

Drugs targeting IgE (omalizumab), IL-5 (mepolizumab, reslizumab, benralizumab), the IL-4–IL-13 pathway (dupilumab) or the most recent antithymic stromal lymphopoietin agent tezepelumab have revolutionized severe T2 asthma. However, patients with ABO or neutrophilic asthma (often T2-low) are 'non-responders' to these biologics as their disease is driven by a different pathway.[23]

Long-term macrolides

Antibiotics like azithromycin, used at sub-therapeutic doses, are recommended for exacerbation reduction in bronchiectasis. Their benefit is thought to be partially anti-inflammatory and immuno-modulatory not just antibacterial. However, they carry significant burdens, including auditory side-effects (hearing loss), QTc prolongation and the substantial long-term risk of promoting antimicrobial resistance.[24,25]

Bronchodilators

Bronchodilators (long-acting beta-agonists (LABA) and long-acting muscarinic antagonists (LAMA)) are key bronchodilators for COPD, with dual LABA/LAMA therapy being more effective than monotherapy for improving lung function and reducing exacerbations in moderate-to-severe cases.[26] For asthma, LAMAs are typically used as an add-on therapy to ICS and LABAs are used for severe cases and in patients with persistent airflow limitation, rather than being a primary treatment.[27,28] Treatment with bronchodilators, such as LAMA or LABA, has been shown to be effective in improving lung function in patients with bronchiectasis and concomitant bronchial obstruction, regardless of other treatments that improve lung function.[29] These data may support the use of LAMA and LABA in patients with bronchiectasis.

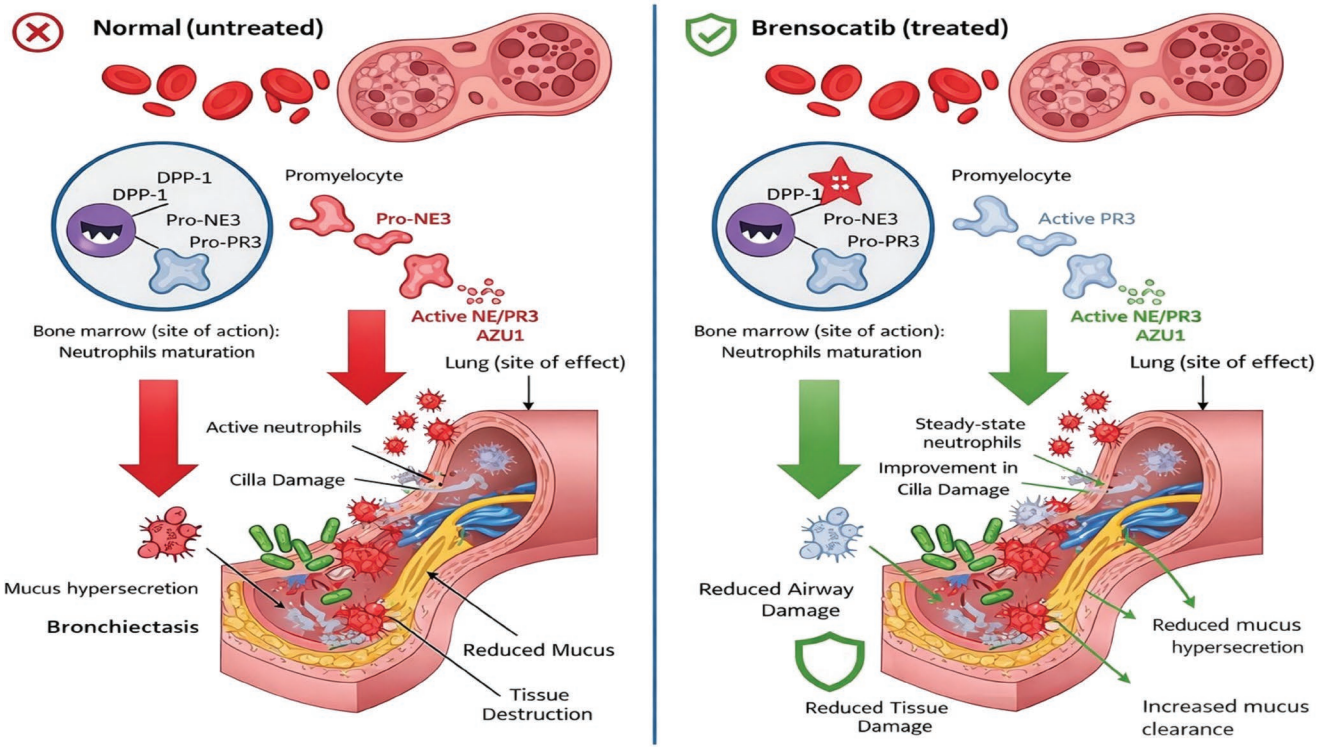
These drugs are therefore essential for managing the symptom of dyspnoea, but in this context, they have little more than a palliative effect. They do not reduce the underlying inflammation, slow down tissue destruction, nor break the vicious cycle. This leaves a serious therapeutic gap, as patients with neutrophil overlap syndromes have not been able to benefit from any therapy to date, highlighting the urgent need for targeted, disease-modifying treatments.

A new paradigm: targeting the source with brensocatib (DPP1 inhibition)

Instead of trying to manage the downstream consequences of inflammation, brensocatib (formerly INS1007) is a first-in-class, oral, reversible inhibitor of DPP1.[30] Its mechanism is a novel 'upstream' intervention (Figure 1). The 'upstream' mechanism of actionintillialy involves DPP1 (also called cathepsin C) as the 'master activator'. DPP1 is a cysteine protease found almost exclusively within the bone marrow, specifically in the azurophilic granules of developing neutrophil precursors (promyelocytes).[31] The sole function of DPP1 is the activation of NSPs; this is achieved by cleaving the inactive proenzymes (pro-NE, pro-PR3, pro-CatG) into their final, active and destructive forms before the neutrophil is released into circulation.[31] Brensocatib administration stops this activation step by binding to and inhibiting DPP1, resulting in 'disarmed' neutrophils: whilst the bone marrow continues to produce a normal number of neutrophils and these neutrophils mature and traffic to sites of infection (like the lungs) normally, when they arrive, their granules contain almost no active NSPs — they are effectively 'disarmed'.[32]

This mechanism of action is profoundly different from other anti-inflammatory therapeutic options as it does not block neutrophil recruitment (like C-X-C motif

Figure 1. Mechanism of action of brensocatib.



(Left Panel) In normal neutrophilic maturation, dipeptidyl peptidase 1 (DPP1) within bone marrow promyelocytes activates inactive pro-neutrophil serine proteases (pro-neutrophil elastase (pro-NE), pro-proteinase 3 (pro-PR3)) into active forms. These activated neutrophils migrate to the lung, where their release of active NE and PR3 drives the vicious vortex of airway damage, mucus hypersecretion, impaired ciliary function, structural remodelling (bronchiectasis), and frequent exacerbations, leading to progressive decline in forced expiratory volume in 1 second. (Right Panel) Brensocatib inhibits DPP1 in the bone marrow, preventing the activation of pro-neutrophil serine proteases. Neutrophils still mature and migrate to the lung but they are 'disarmed' of their destructive enzymes. This leads to reduced tissue damage, diminished mucus hypersecretion, preserved airway structure, and an interruption of the vicious vortex, resulting in fewer exacerbations and a slowing of decline in forced expiratory volume in 1 second. AZU1, azurocidin 1.

chemokine receptor 2 (CXCR2) inhibitors, which have had mixed results), kill circulating neutrophils (neutropenia), nor block the T2 pathway (like biologics).[33] Brensocatib simply reduces the destructive payload of the neutrophils, allowing them to perform other functions (like phagocytosis) whilst minimizing the collateral damage that drives the vicious vortex. The hypothesis is that, by reducing the burden of active NE, PR3 and CatG in the airways, brensocatib can slow tissue destruction, reduce mucus hypersecretion and, ultimately, break the cycle of exacerbations and lung function decline.[34]

The clinical evidence: from WILLOW to ASPEN

The clinical development programme for brensocatib has provided robust evidence for this hypothesis in the core population of patients with bronchiectasis, which inherently includes the overlap phenotypes.

Phase II: the WILLOW trial

The WILLOW trial was a 24-week, randomized, placebo-controlled, phase II study involving 256 patients with NCFBE.[35] It was designed to find the optimal dose and establish proof-of-concept. The trial had two fundamental objectives, namely establish proof of mechanism to demonstrate that brensocatib, a DPP1 inhibitor, could successfully and measurably reduce its downstream target — active NE — in the sputum of patients, and establish proof of concept to see if this reduction in NE translated into a meaningful clinical benefit, specifically a reduction in the frequency of pulmonary exacerbations.

The WILLOW study, which tested two doses (10 mg and 25 mg) against placebo, was highly successful, meeting its primary and key secondary endpoints. The trial's primary endpoint was the time to the first pulmonary exacerbation over the 24-week treatment period. Both brensocatib doses significantly prolonged the time to first exacerbation compared to placebo: 10 mg dose: 42% risk reduction (hazard ratio (HR) 0.58; p=0.029) and 25 mg dose: 38% risk reduction (HR 0.62; p=0.046). This was the first clear clinical signal that this novel mechanism could impact a patient-centric outcome. The secondary (mechanistic) endpoint was the reduction of sputum NE; this was arguably the most important scientific finding of the WILLOW trial. Brensocatib demonstrated a significant, dose-dependent reduction in the concentration of active NE in sputum: the 10 mg dose showed a significant reduction *versus* placebo (p=0.034) and the 25 mg dose a numerically greater, significant reduction *versus* placebo (p=0.021). This finding provided the crucial mechanistic validation (proof of mechanism). It confirmed that the drug was reaching its target in the bone marrow (DPP1) and successfully 'disarming' the neutrophils, leading to less active NE in the target organ (the lungs).

Furthermore, subsequent analyses showed that patients who achieved complete NE suppression (below the level of quantification) in their sputum had the lowest risk of future exacerbations, directly linking the mechanism to the clinical benefit. The 10 mg dose significantly reduced the AER by 36% (p=0.041). The 25 mg dose showed a 25% reduction, which was not statistically significant (p=0.167). This created an interesting dose–response question. Whilst the 25 mg dose showed a stronger mechanistic effect (greater NE reduction), the 10 mg dose showed a stronger clinical effect in this shorter, 24-week study. This ambiguity in the optimal dose was a key reason a larger, longer-term phase III trial was necessary.

The WILLOW trial was a pivotal moment in bronchiectasis research for several reasons: it was the first study to prove that inhibiting DPP1 could be a viable therapeutic strategy in NCFBE, thus validating a new therapeutic class, and it moved the field's focus from antibiotics (targeting infection) to neutrophil modulation (targeting inflammation). Furthermore, it linked the mechanism to clinical benefit by showing that reducing NE (the mechanism) led to fewer exacerbations (the benefit), providing a strong rationale for larger-scale development. Finally, it informed the phase III design: the success of WILLOW gave the green light for the phase III ASPEN trial. However, the slightly confusing dose–response (10 mg *versus* 25 mg) results highlighted the need to retest both doses in a much larger, 52-week study. It was hypothesized that the more potent 25 mg dose might show its true benefit over a longer period, especially concerning the progressive nature of lung function decline — an end point, the 24-week WILLOW study was too short to assess.

In essence, WILLOW provided the 'why', and ASPEN provided the 'how much'. WILLOW proved the concept that disarming neutrophils was clinically beneficial, whilst the subsequent ASPEN trial (as we discussed) defined the magnitude of that benefit, identifying the 25 mg dose as the one capable of not just reducing exacerbations but also modifying the long-term, progressive course of the disease (lung function decline).

Phase III: the ASPEN trial

The phase III ASPEN trial, a 52-week, global, randomized, double-blind, placebo-controlled study, evaluated the efficacy and safety of the oral DPP1 inhibitor brensocatib in 1,721 patients (1,680 adults and 41 adolescents) with NCFBE who had experienced at least two pulmonary exacerbations in the prior 12 months.[5] The trial met its primary endpoint, with both brensocatib 10 mg and 25 mg doses demonstrating a statistically significant reduction in the AER compared to placebo. Critically,

the 25 mg dose also met a key secondary endpoint by showing a statistically significant slowing of lung function decline, as measured by post-bronchodilator FEV_1. These findings represent the first phase III evidence of a therapy not only managing exacerbations but also exhibiting disease-modifying effects by preserving lung function in NCFBE. Patients were randomized (1:1:1 in adults) to receive brensocatib 10 mg, brensocatib 25 mg, or matching placebo, administered orally once daily for 52 weeks. The primary efficacy endpoint was the AER over the 52-week treatment period. The key secondary endpoints were tested hierarchically and included time to first exacerbation, the proportion of patients remaining exacerbation-free, and the change from baseline in post-bronchodilator FEV_1 at 52 weeks.

The ASPEN trial successfully met its primary and key secondary endpoints. Both doses of brensocatib significantly reduced the rate of pulmonary exacerbations compared to placebo: brensocatib 10 mg: 21.1% reduction (AER 1.02 *versus* 1.29 for placebo; p=0.004) and brensocatib 25 mg: 19.4% reduction (AER 1.04 *versus* 1.29 for placebo; p=0.005). Both doses also significantly prolonged the time to first exacerbation and increased the proportion of patients who remained exacerbation-free over 52 weeks (48.5% for both doses *versus* 40.3% for placebo) (Table 2).

Regarding key secondary endpoints, the analysis of lung function preservation provided the trial's most significant finding: the placebo group exhibited a mean FEV_1 decline of -62.3 mL over 52 weeks, consistent with the known natural history of this 'frequent exacerbator' population. The brensocatib 10 mg group showed a non-significant trend towards preservation (decline of -50.0 mL) whilst the brensocatib 25 mg group demonstrated a mean FEV_1 decline of only -24.2 mL. This represents a statistically significant slowing of FEV_1 decline by 38.1 mL *versus* placebo (p=0.0054). The effect on lung function was further supported by a significant preservation of forced vital capacity in the 25 mg group (a 75.3 mL benefit *versus* placebo; p<0.0001). Patients in the 25 mg arm also reported a statistically significant improvement in quality of life (QOL-B Respiratory Symptom Score).

Brensocatib was generally well tolerated with a favourable safety profile. The most common treatment-emergent adverse events (e.g. cough, headache and nasopharyngitis) were largely comparable to placebo. Importantly, there was no observed increase in the rate of severe infections or pneumonia, allaying theoretical concerns about modulating neutrophil function.

In light of these outcomes, the ASPEN trial results are a significant milestone in NCFBE management. Whilst the reduction in exacerbations is clinically meaningful and comparable to existing (off-label) therapies like macrolides, the FEV_1 data is potentially transformative. This is the first pivotal trial in NCFBE to demonstrate disease modification. The 38 mL per year preservation of FEV_1 in the 25 mg arm is highly statistically and clinically significant (the minimum clinically important differences for

Table 2. Summary of phase III clinical trial findings for brensocatib (ASPEN).

Endpoints/measures	Placebo (n=542)	Brensocatib 10 mg (n=533)	Brensocatib 25 mg (n=532)	p value (vs placebo)
Annualized rate of pulmonary exacerbations (primary)	1.29	1.02	1.04	<0.001
Reduction vs placebo	–	21.1%	19.4%	
Time to first exacerbation	Shorter	Longer	Longest	<0.001
Change in post-BD FEV_1 (mL) at week 52 (Key secondary)	-28.9	-28.7	-24	0.047
Slowing of FEV_1 decline vs placebo	–	0.7%	38.1%	
Adverse events (any)	85.1%	89.1%	88.0%	NS
SAE	15.1%	19.1%	18.2%	NS
On-target skin/oral AEs	Low	Higher	Higher	
Pneumonia (SAE)	2.2%	1.9%	2.1%	NS

Note: Data derived from primary publications and presentations of the ASPEN trial; p values represent statistical significance compared to placebo. AEs, adverse events; FEV_1, forced expiratory volume in 1 second; Post-BD, post bronchodilator; SAE, serious adverse events.

FEV_1 is 100 mL, as it represents a slowing of the disease's progressive, structural decline by over 60%.[36] It should be noted that the post-bronchodilator mean FEV_1 in litres was 1.65 in patients colonized with *P. aeruginosa* and 2.09 in those who were negative at baseline. These are, therefore, patients who already showed significant respiratory impairment at baseline. Comparing this annual FEV_1 preservation data with the natural history of COPD decline (up to -60 mL/year) helps to better understand the magnitude of the benefit that can be achieved for this patient population.[37]

This finding validates the 'vicious cycle' hypothesis and provides strong evidence that targeting the underlying neutrophilic inflammation (specifically, by inhibiting DPP1 to reduce active NE) can protect the lung from the inexorable damage that defines the disease.

Whilst the 10 mg dose controls exacerbations, the 25 mg dose appears to be necessary to achieve the disease-modifying effect (in particular, the preservation of FEV_1). This is the key point about the 'disease-modifying' effect, resulting from maximum NE suppression, which is best achieved with the 25 mg dose and is related to structural preservation.

The ASPEN trial confirms brensocatib as a potential first-in-class therapy for NCFBE. By demonstrating both a significant reduction in exacerbations and, for the first time, a robust slowing of FEV_1 decline, brensocatib is poised to shift the treatment paradigm from symptom suppression to true disease modification. Pending regulatory approval, brensocatib 25 mg may become a foundational therapy for patients with NCFBE, aimed at altering the long-term trajectory of this progressive disease.

Perspectives on the overlap syndromes: what ASPEN means for BCOS

The ASPEN trial's broad population provides direct and inferred evidence for the utility of brensocatib in the difficult-to-treat overlap phenotypes. The ASPEN trial enrolled a significant number of patients with a concomitant diagnosis of COPD (representing the BCOS phenotype). Subgroup analyses, including those presented at CHEST 2025,[38] have confirmed (1) consistent efficacy—the treatment effect of brensocatib in reducing exacerbations was maintained in the BCOS subgroup; this high-risk group, which typically exacerbates frequently, received a benefit consistent with the overall population, and (2) lung function preservation: critically, the signal for slowing FEV_1 decline was also observed in the BCOS subgroup for the 25 mg dose. This is clinically profound, as these patients experience the 'double-hit' of lung function loss from both COPD and bronchiectasis. The data suggests that brensocatib 25 mg may offer the first pharmacological means to decelerate this trajectory in patients who continue to exacerbate despite optimized standard-of-care.

Thus, brensocatib has the mechanistic rationale to be a potential first-line, targeted therapy for patients with BCOS that continues to exacerbate despite optimized LAMA/LABA/ICS therapy. However, it should be reiterated that, although the biology (neutrophils) is common, clinical trials relating to ABO and BCOS specifically require a dedicated study or the publication of *post hoc* analyses.

Inferred and plausible evidence: ABO

The ASPEN trial population also included a substantial number of patients with a history of asthma (approximately 18–20%).[5] Whilst specific subgroup data for ABO is less detailed than for BCOS, the biological rationale is exceptionally strong.

- Targeting the endotype: Severe asthma is not a monolith. Patients with asthma who develop bronchiectasis (ABO) are frequently those with a non-T2, neutrophilic or mixed-inflammatory endotype. These are the 'difficult-to-treat' patients with asthma in whom treatment with high-dose ICS and T2-biologics fails.
- A 'non-biologic' targeted therapy: Brensocatib offers the first oral, targeted therapy for this specific neutrophilic endotype of severe asthma. For patients with ABO with a sputum profile high in neutrophils and active NE (and low in eosinophils), brensocatib is a precision medicine approach.
- Consistency of effect: Public statements regarding the ASPEN trial have noted that the treatment effect was consistent across the 'vast majority' of pre-specified subgroups, which would include the asthma history subgroup.

The clinical profile: safety and tolerability

A novel mechanism often brings a novel side-effect profile, and DPP1 inhibition is no exception. A balanced review must consider its tolerability.

On-target cutaneous effects

DPP1 is also expressed in epithelial tissues, particularly the skin (especially palms and soles) and gums. Therefore, inhibition can lead to palmoplantar keratoderma and other skin rashes such as mild-to-moderate rashes or scaling. These effects are generally dose-dependent, mild-to-moderate and reversible upon dose reduction or cessation.

Dental and gingival events

DPP1 deficiency is genetically linked to Papillon–Lefèvre syndrome (which causes tooth loss).[39] Clinical trials monitored this closely and found no major periodontal

concern over 52 weeks, but it remains an area of watchfulness. Periodontal inflammation, gingivitis and dental infections have been noted as an adverse event class. This requires patients on brensocatib to maintain good oral hygiene and regular dental follow-up. Further studies on the dental effects of brensocatib showed that the progression of periodontal disease, measured by periodontal pocket depth, was similar in both the treated and placebo groups, and gingival inflammation scores improved in both groups, possibly also due to regular follow-up by the dentist during the trial.[40]

Infection risk

A theoretical concern was whether 'disarming' neutrophils would increase the risk of infections. The WILLOW and ASPEN trials were reassuring. They did not show a clinically significant increase in the overall rate of infections or pneumonia. This is a key differentiator from broad immunosuppressants or corticosteroids. Neutrophils can still traffic, phagocytose and signal; they just cause less collateral damage.[5,35]

The safety signal in the BCOS subgroup analysis (as noted at CHEST 2025) did show a higher rate of SAEs in the brensocatib arms.[35] However, this must be contextualized: the BCOS population is inherently sicker, older and more frail than the non-BCOS bronchiectasis population, and thus has a much higher baseline rate of SAEs. The data warrants careful risk–benefit calculation in this frail population but does not negate the powerful efficacy signal. From a practical standpoint, it may be useful for physicians to consider recommendations based on trial protocols, for example, recommending regular dental screening or managing skin effects by interrupting the dose rather than discontinuing it permanently.

Future horizons in asthma and COPD

Bronchiectasis can be a primary diagnosis but is frequently a secondary diagnosis resulting from another chronic lung disease such as COPD, emphysema, interstitial lung diseases or cystic fibrosis. The distinction between COPD and asthma caused by primary bronchiectasis is based on fundamental clinical details that are not always easy to distinguish and interpret, given the considerable heterogeneity of phenotypes.[41,42] COPD rarely occurs in the absence of a history of smoking. Non-smokers with chronic cough, sputum production and wheezing require alternative diagnoses to be ruled out. Asthma typically occurs during childhood or early adulthood, often with a family history of atopy. Asthma-like symptoms that arise in late adulthood without a T2 high endotype require evaluation for bronchiectasis. Ultimately, the development of increased cough and sputum volume/purulence in patients known to have asthma or COPD should prompt consideration of secondary bronchiectasis. Identification of bronchiectasis may allow therapeutic modifications to improve outcomes (Table 3).

A HRCT scan is the gold standard for diagnosing bronchiectasis and differentiating the structural changes. Key findings include signet ring sign: a thickened bronchial wall adjacent to an artery, where the airway lumen is larger than the vessel (like a ring on a finger); tram track or tram line sign: thickened, parallel airway walls; and mucoid impaction (tree-in-bud pattern): airways plugged with mucus. In COPD (emphysema), HRCT shows areas of low attenuation (darker areas) due to the destruction of the alveolar walls, indicating emphysema, and airway wall thickening may also be present due to chronic bronchitis.[43] In asthma, HRCT findings are often normal in mild disease, whereas in severe asthma, it may show bronchial wall thickening and air trapping (areas that appear darker on expiration-phase scans).[40]

In overlap syndromes, the coexistence of features from two or more conditions is known as ACO or simply overlaps with bronchiectasis. The overlap of COPD–bronchiectasis is highly prevalent (up to 50% in some cohorts with severe COPD). Patients typically have worse symptoms,

Table 3. Potential of brensocatib in COPD and asthma.

Feature	Bronchiectasis (NCFBE)	COPD and asthma
Status	Approved (2025)	Investigational/potential
Evidence	Validated by phase III ASPEN trial showing reduced exacerbations (-20%) and slowed lung function decline	Mechanism is sound for neutrophilic COPD and asthma, but large-scale phase III trials specifically for these indications are not yet completed/published with the same positive outcomes as bronchiectasis
Key benefit	Breaks the 'Vicious Vortex' of infection → inflammation → damage	Could potentially slow disease progression (emphysema/remodelling)

COPD, chronic obstructive pulmonary disease.

more severe airflow obstruction, more frequent exacerbations and higher rates of colonization with pathogenic organisms like *P. aeruginosa*.[44] In the overlap of asthma–bronchiectasis, bronchiectasis is more common in patients with severe, uncontrolled asthma, chronic sputum production and frequent infections, suggesting the severe inflammation has led to permanent airway damage.[45] In all cases, identifying the 'treatable traits', such as chronic infection (bronchiectasis), eosinophilic inflammation (asthma) or fixed obstruction (COPD), is the goal of a thorough diagnostic workup.

The emergence of brensocatib is more than just a new drug for bronchiectasis; it is a validation of a new therapeutic approach for all neutrophilic-driven lung diseases. It forces a fundamental shift in the management of severe obstructive disease.

From symptom control to disease modification

For the first time, in a robust phase III trial, a therapy has shown an ability to slow FEV_1 decline in this population.[5] This moves the therapeutic goal from simply 'managing the next exacerbation' to 'preserving the patient's future lung function'. This leads to a new diagnostic imperative—the interesting clinical data on brensocatib will likely prompt pulmonologists to modify their clinical practice. For a patient with frequent exacerbations of COPD or 'difficult-to-treat' asthma, the new standard of care will likely need to answer two questions: Does this patient have underlying bronchiectasis? (prompting more judicious use of HRCT scanning), and what is their inflammatory endotype? (prompting a new focus on biomarkers and sputum analysis for neutrophils and active NE).

The rise of biomarker-driven therapy

The future of brensocatib therapy will likely be in precision medicine. Sputum-active NE, used as a 'proof-of-mechanism' biomarker in the WILLOW trial, could become the 'proof-of-selection' companion diagnostic.[34] A patient with high sputum NE would be an ideal candidate, whilst one with low NE may not benefit.

Unanswered questions

The field is now wide open. Future studies must explore the role of brensocatib in bronchiectasis due to other causes (like rheumatoid arthritis), its long-term safety beyond 1 year, and its potential in other neutrophilic diseases (e.g. cystic fibrosis, hidradenitis suppurativa and ANCA-vasculitis).[46]

In summary, the complex overlap of asthma, COPD and bronchiectasis creates a severe phenotype that has, until now, eluded effective, targeted therapy. By identifying the neutrophilic 'vicious vortex' as the common enemy and DPP1 inhibition as the strategic target, brensocatib provides a long-awaited, mechanism-based and disease-modifying oral therapy that will fundamentally reshape the management of chronic inflammatory lung disease. Brensocatib could therefore have the potential to be not only a drug for bronchiectasis but also a first targeted therapy for the 'treatable neutrophil tract' across the entire spectrum of airway diseases.

This promising therapeutic strategy will not be limited to brensocatib in the future but will likely see the arrival of additional promising therapeutic options that are currently in clinical development (Table 4).[47,48]

Usefulness of brensocatib for COPD

COPD is classically driven by neutrophilic inflammation (unlike 'allergic' asthma, which is eosinophilic). NE is the primary enzyme responsible for breaking down elastin, the protein that keeps lungs elastic. This destruction leads to emphysema. By reducing NE activity, brensocatib could theoretically slow the structural progression of emphysema.[49] Additionally, NSPs stimulate mucus glands to grow and overproduce mucus (chronic bronchitis). Blocking them could reduce mucus plugging, improving airflow and reducing the chronic cough.[50] Finally, COPD exacerbations are often triggered by a spike in neutrophil activity. The ASPEN trial proved that brensocatib significantly reduces exacerbations,[5] suggesting that a similar benefit could translate to patients

Table 4. Phase II trials on new DPP1 inhibitors.

Drug name	Development stage/ trial name	Target population	Key finding
HSK31858	Phase II SAVE-BE (Completed)	Chinese patients with NCFBE	Demonstrated comparable efficacy in reducing exacerbation risk by 48–59%
Verducatib (BI 1291583)	Phase II Airleaf (Completed)	Patients with NCFBE	DPP1/CatC inhibitor Showed treatment reduced the risk of bronchiectasis exacerbations

BE, bronchiectasis; DPP1/CatC, dipeptidyl peptidase 1/cathepsin C; NCFBE, non-cystic fibrosis bronchiectasis.

with COPD, particularly 'frequent exacerbators' who have high neutrophil levels (Table 5).

Usefulness of brensocatib for asthma

Brensocatib is unlikely to be effective for typical T2 asthma without bronchiectasis. It is potentially useful for a specific, difficult-to-treat subtype: neutrophilic/T2 low asthma (Table 5). Approximately 5–10% of patients with asthma have severe neutrophilic asthma and often do not respond well to inhaled corticosteroids because their inflammation is driven by neutrophils, not eosinophils. Currently, there are very few targeted therapies for this group of patients.[51] Just as in COPD, NSPs in severe asthma damage the airway lining and cause scarring (remodelling). Brensocatib could prevent this permanent airway thickening.[52] Existing asthma biologics target T2 inflammation (IgE, IL-5, IL-4–IL-13). Brensocatib targets the innate immune system (neutrophils), offering a completely new pathway for patients in whom all other biologic therapies have failed.[53]

Conclusion

The management of chronic obstructive lung diseases, historically viewed as separate entities like asthma and COPD, is converging on a shared, critical path: persistent, neutrophil-dominant airway inflammation. This inflammatory state is the common mechanism fuelling the severe, difficult-to-treat phenotypes seen in overlap syndromes such as ABO and BCOS. The central factor is the 'vicious vortex' of infection, inflammation and structural damage, driven by the destruction caused by NSPs, especially NE. Traditional cornerstone therapies, like ICS and T2-targeted biologics, are often ineffective in this non-T2, neutrophilic environment, highlighting a significant therapeutic gap. The emergence of brensocatib, a first-in-class, oral, reversible inhibitor of DPP1, offers a novel, targeted and disease-modifying strategy.

Brensocatib is poised to fundamentally reshape the clinical paradigm of chronic inflammatory lung disease by identifying a common pathogenic endotype and providing a targeted oral therapy to break the destructive cycle. Its success necessitates a new diagnostic imperative, prompting pulmonologists to utilize HRCT, blood and sputum biomarkers to identify the underlying bronchiectasis and the neutrophilic or mixed endotype in patients with frequently exacerbating COPD and difficult-to-treat asthma.

Table 5. Potential patient characteristics for brensocatib eligibility based on a 'treatable traits' approach.

Category	Characteristic/criterion	Rationale and clinical evidence
Core diagnosis	NCFBE	The primary indication validated by the phase III ASPEN trial
Exacerbation history	'Frequent exacerbator' phenotype	Patients with a history of ≥2 pulmonary exacerbations in the prior 12 months This group showed significant benefit in reduced AER in clinical trials
Lung function status	Progressive decline	Patients showing rapid lung function loss; the 25 mg dose specifically demonstrated a statistically significant slowing of FEV_1 decline (disease modification)
Overlap phenotype: BCOS	COPD with bronchiectasis	Patients with COPD who have confirmed bronchiectasis and continue to exacerbate despite optimized standard-of-care (LAMA/LABA/ICS) Subgroup analysis showed consistent efficacy in this high-risk group
Overlap phenotype: ABO	Severe neutrophilic asthma	Patients with severe asthma and bronchiectasis who are non-responders to T2-biologics (e.g. anti-IL-5/IgE) or ICS due to a non-eosinophilic, neutrophil-dominant endotype
Inflammatory endotype	High sputum NE	A potential 'proof-of-selection' biomarker Patients with high active NE levels in sputum are mechanically ideal candidates, as brensocatib targets this specific enzyme
Demographics	Adults and adolescents	The ASPEN trial successfully enrolled and evaluated both adults (n=1,680) and adolescents (n=41)

ABO, asthma–bronchiectasis overlap; AER, annualized exacerbation rates; BCOS, bronchiectasis–COPD overlap syndrome; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; IgE, immunoglobulin E; LABA, long-acting beta-agonists; LAMA, long-acting muscarinic antagonists; NCFBE, non-cystic fibrosis bronchiectasis; NE, neutrophil elastase.

In this regard, it will be interesting and essential to define its effectiveness in patients with chronic obstructive disease with low T2 endotype, with or without the presence of bronchiectasis. Specifically, the 25 mg dose has demonstrated the ability to slow lung function decline, offering the first potential disease-modifying therapy for NCFBE and its severe overlap syndromes. This requires a new diagnostic imperative: actively identifying the 'treatable traits' of bronchiectasis and neutrophilic inflammation in patients with the most difficult-to-treat respiratory disease. For patients with asthma, ACO or COPD with a T2-high or mixed endotype and bronchiectasis as a comorbidity, it would be interesting to hypothesize treatment regimens that combine biologics and brensocatib to control complex clinical conditions when a single treatment option is insufficient.[54,55] Any positive evidence could drastically change the current treatment paradigm for diseases that can currently be defined as almost 'orphan'.

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