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DRUG PROFILE

A profile of brensocatib for non-cystic fibrosis bronchiectasis

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ABSTRACT

Introduction: Non-cystic-fibrosis bronchiectasis (NCFB) is an airway disorder with a growing worldwide prevalence that affects predominantly older and female individuals and is associated with high symptom burden and significant healthcare expenditure. Brensocatib is a novel orally bioavailable, selective, and reversible dipeptidyl peptidase 1 (DPP1) inhibitor that leads to a sustained inhibition of neutrophil serine protease activity in both whole blood and sputum.

Areas covered: This drug profile summarizes the role of inflammation in the pathophysiology of bronchiectasis. The mechanism of action of brensocatib in reducing neutrophil-related inflammation is described. We then summarize existing efficacy and safety data from Phase 2 and Phase 3 studies of brensocatib in patients with bronchiectasis, in which the rate of exacerbation was the primary endpoint. Finally, we summarize the current marketplace for brensocatib, including the unmet for effective therapies for bronchiectasis, and the status of other potential treatments undergoing clinical trials.

Expert opinion: Brensocatib is a first-in-class DPP1 inhibitor that shows promise as a treatment for patients with bronchiectasis.

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KEYWORDS
Bronchiectasis; brensocatib; dipeptidyl peptidase inhibitor; neutrophil serine protease; inflammation; exacerbation; treatment; anti-inflammatory

1. Introduction

Bronchiectasis that is not due to cystic fibrosis (CF) – also known as non-CF bronchiectasis and from here on in this article referred to simply as bronchiectasis – is a condition characterized by impaired mucociliary function of the airways, retention of thick (frequently infected) mucus, and ultimately permanent airway dilatation responsible for the name 'bronchiectasis' (Greek: bronkhos (airway) and ekstasis (dilation or expansion)) [1]. Bronchiectasis may result from or be associated with a number of conditions such as chronic or severe infection (e.g. tuberculosis or non-tuberculous mycobacteria), immunodeficiency (e.g. common variable immunodeficiency), hyperactive immune system (e.g. allergic bronchopulmonary aspergillosis, rheumatoid arthritis, and inflammatory bowel disease), primary (i.e. primary ciliary dyskinesia) or secondary (e.g. pathogen-induced [2]) impairment of mucociliary clearance apparatus, as well as predisposing anatomical abnormalities (e.g. congenital cartilaginous airway deficiency). A significant percentage of patients with long-standing, severe asthma or chronic obstructive pulmonary disease (COPD) will also develop bronchiectasis. Approximately 40% of patients with bronchiectasis have no identifiable cause or associated condition.

Common clinical manifestations of bronchiectasis include cough, sputum production, dyspnea, and fatigue. Other reported symptoms include wheezing, chest discomfort, hemoptysis, fever, weight loss, loss of appetite, and sweating [3]. Clinical course is often punctuated by exacerbations characterized by sudden appearance of new or increased severity of the preexisting symptoms of cough and sputum volume or purulence, which may be accompanied by fever, dyspnea, hemoptysis, or fatigue. This constellation of symptoms, unless transient (i.e. lasting less than 48 h), typically requires treatment with antibiotics and adjunctive therapies and may result in hospitalization depending on the severity of the illness. Cough, sputum production, bronchiectasis exacerbations, fatigue, and dyspnea are the most common disease manifestations with a negative effect on the patient's quality of life [4]. Like other chronic airway diseases such as COPD, exacerbations of bronchiectasis are associated with increased disease severity and worse prognosis, as well as with increased healthcare utilization and costs [5]. Consequently, frequency of exacerbations is currently the most common primary end point in clinical trials of bronchiectasis therapies.

According to the 'vicious vortex' framework, mucus clearance abnormalities, infection, and inflammation synergistically contribute to disease severity and progression [6]. Mucus retention results from a combination of hypersecretion of thick mucus and impaired function of the cilia on the luminal surface of bronchial epithelial cells. Infection with biofilm-forming bacteria, such as *Pseudomonas aeruginosa*, often develops in the course of illness, while non-tuberculous mycobacterial infection may precede or follow bronchiectasis development. Regardless of the presence of infection, chronic neutrophilic airway inflammation is a hallmark of bronchiectasis [6,7], although approximately 20% have an eosinophilic (blood eosinophil counts of ≥300 cells/μl) phenotype associated with airway eosinophilia and short time to exacerbation [7].

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Neutrophils – the most abundant leukocytes in circulation – represent the first line of defense against invading pathogens [8]. Neutrophil serine proteases (NSPs), such as neutrophil elastase (NE), are stored in azurophilic granules that, upon neutrophil activation and degranulation, are released into the target tissue where they participate in the killing of extracellular pathogens and regulation of immune response [9]. Neutrophils develop from precursor cells (myeloblasts) in the bone marrow for ~12–18 days prior to entering circulation. Before being packaged into granules, the inactive form (zymogen) of NSPs is activated by an enzyme called dipeptidyl peptidase 1 (DPP1). DPP1, also known as cathepsin C, cleaves the N-terminal dipeptide sequence of the NSP zymogen during the first days of neutrophil development [10], thereby creating the active enzyme.

While protective under normal conditions, NSPs do not appear to be essential for host defense, as manifested in patients with a rare autosomal recessive condition of DPP1 absence – Papillon-Lefevre syndrome (PLS) [11]. People affected by this condition exhibit a nearly complete absence of DPP1 function and NSP activity – yet do not suffer from severe infections, although they are prone to severe destructive periodontal disease and skin hyperkeratosis manifesting with redness and thickening of the skin of palms and soles. Other manifestations include hyperhidrosis, arachnodactyly, intracranial calcification, and intellectual disability. And while systemic infection is uncommon, immune dysfunction in PLS patients has been described: e.g. reduced in vitro neutrophil response to *Staphylococcus* spp. and impairment of natural killer cell cytotoxic function [12].

Unlike low NSP activity, high levels of NSPs have been associated with excessive inflammatory airway damage and mucus hypersecretion [13–15]. In a study by Chalmers and colleagues, sputum neutrophil elastase activity was correlated with bronchiectasis severity index, greater dyspnea, lower forced expiratory volume in 1 s (FEV1), and greater radiographic extent of disease [16]. Consequently, targeting DPP1-NSP pathway is an attractive approach to the treatment of airway diseases characterized by neutrophilic inflammations, such as bronchiectasis.

2. Overview of the market

Bronchiectasis was once thought of as an orphan disease, however its prevalence in the U.S. alone is now estimated to be above 500,000 [17]. Furthermore, a rising prevalence has been documented over the past two decades [18]. For comparison, CF and idiopathic pulmonary fibrosis (IPF) are each estimated to be only 1/10th as common [19,20]. Bronchiectasis disproportionately affects women and older individuals [17].

Treatment approaches aim to break the 'vicious vortex' of bronchiectasis, reduce the frequency of exacerbations, and improve the quality of life. Several expectoration techniques (e.g. active cycle of breathing, huff coughing, etc.), mucus clearance devices (e.g. oscillating positive airway pressure or high-frequency chest wall oscillating devices), and mucoactive substances (e.g. inhaled hypertonic saline) have been developed. Both systemic and inhaled antibiotics are in use to treat airway infection. A recent meta-analysis demonstrated that long-term (4 weeks or longer) inhaled antibiotics were associated with a small reduction in exacerbation frequency (rate ratio [RR], 0.78; 95% CI, 0.68–0.91) and a slight improvement in quality of life [21].

Anti-inflammatory treatment options, however, are extremely limited. Inhaled corticosteroids (ICS) are not recommended for the treatment of bronchiectasis in the absence of an accompanying condition (such as asthma) with approved indications [22] and have been associated with an increased risk of bacterial and mycobacterial infections in this patient population [23], although emerging evidence suggests that they may be useful in bronchiectasis patients with an eosinophilic phenotype even in the absence of asthma [24]. Daily or thrice weekly azithromycin is the only medication recommended by the European Respiratory Society and British Thoracic Society guidelines for its dual anti-bacterial and, more importantly, anti-inflammatory action. Several meta-analyses confirmed that long-term macrolide therapy (typically azithromycin) may lead to a significant reduction in the frequency of exacerbations and improved quality of life, albeit at a cost of potential microbial macrolide resistance and a risk of cardiovascular adverse events [25,26].

Despite aggressive treatment including airway clearance, chronic macrolide therapy and/or inhaled antibiotics, patients with bronchiectasis often have poor quality of life, frequent exacerbations, and an inexorable decline in lung function[3] [3]. For example, inhaled antibiotics result in only a small decrease in exacerbation frequency and a minimal improvement in quality-of-life measures [21]. Thus, there remains a large unmet need for the treatment of this condition

No treatment specific to neutrophil-driven inflammation has been available. In fact, no bronchiectasis-specific treatment has received approval from the Federal Drug Administration (FDA) or European Medicines Agency (EMA) to date. As of the time of this writing, four DPP1 inhibitors – GSK2793660 (GlaxoSmithKline), HSK31858 (Haisco Pharmaceutical Group Co), BI 1,291,583 (Boehringer Ingelheim), and brensocatib (Insmed) have been evaluated in clinical trials (clinicaltrials.gov). In a phase I study of GSK2793660, the compound failed to significantly reduce plasma neutrophil elastase activity (despite effectively inhibiting whole blood DPP1 activity) and resulted in high incidence (7/10 subjects) of palmar and plantar desquamation – the study was terminated early [27]. A phase II trial of HSK31858 is being performed in China and has completed enrollment (clinicaltrials.gov NCT05601778). The results of a phase II study of BI 1,291,583 have recently been published [28]. It demonstrated a dose-dependent benefit of BI 1,291,583 over placebo with respect to the time to first exacerbation of bronchiectasis.

Of the above compounds, only brensocatib has undergone a phase III clinical trial to date. The rest of this manuscript will focus on the description of this drug, its pharmacokinetics/dynamics, clinical effectiveness, and safety.

3. Introduction to the drug

Brensocatib is a novel orally bioavailable, selective, and reversible inhibitor of DPP1. Its chemical formula is C23H24N4O4. The *in-vitro* negative log of half-maximal inhibitory concentration (pIC50) in humans is ~6.85 (i.e. 50% of DPP1 is inhibited at the concentration of ~0.14 µM [NCBI 2024]). Brenscocatib

absorption follows first-order kinetics, and its clearance is linear [29]. Half-life ($t_{1/2}$) of brensocatib in healthy volunteers is 24.3 h and 26.0 h for the 10 mg and 25 mg doses, respectively [10]. The $t_{1/2}$ in bronchiectasis patients is longer −38.5 h and 39.1 h, respectively, allowing for daily dosing [29]. In the phase II (WILLOW) trial, the steady-state plasma (AUC_t), minimum (C_{min}) and maximum (C_{max}) drug concentrations have been observed to be highly correlated with each other and not significantly affected by age, body weight, or creatinine clearance, indicating that dose adjustment is not necessary for these variables [29].

In the first-in-humans study, healthy volunteers received 10 mg, 25 mg, or 40 mg of daily brensocatib for up to 28 days [10]. Response to treatment – reduction in whole blood neutrophil elastase activity – was observed after ~12 days, consistent with the timeline of neutrophil maturation in the bone marrow. At these doses, the mean steady-state inhibition of whole blood NE activity was 30%, 49%, and 59% respectively.

Sputum NE activity in patients with bronchiectasis is highly variable at baseline (owing to both inter-individual variability in NE levels and sputum sample quality). However, sputum NE levels below the level of quantification (BLQ) were strongly associated with reduced risk of bronchiectasis exacerbation in the WILLOW trial [30]. While no direct relationship between brensocatib exposure (AUC_t) and the risk of bronchiectasis exacerbation was observed, there was a threshold AUC_t for attaining sputum NE levels BLQ. Both 10 mg and 25 mg doses achieved this threshold AUC_t [30]. In addition, no significant relationship between brensocatinib AUC_t and adverse events of special interest (see Safety section below) was detected [30].

4. Clinical efficacy

Initial evidence of the efficacy of brensocatib in bronchiectasis came from a phase II, randomized, double-blind, placebo-controlled trial of brensocatib in bronchiectasis (WILLOW trial) [30]. In it, 256 patients with bronchiectasis were randomized to receive placebo, 10 mg or 25 mg of brensocatib daily for 24 weeks. Exacerbations were defined in accordance with the consensus definition for clinical research [31] as the presence of at least three of the following symptoms – increased cough, increased sputum volume or change in sputum consistency, increased sputum purulence, increased breathlessness or decreased exercise tolerance, fatigue or malaise, and hemoptysis – for at least 48 h, leading to an antibiotic prescription. Severe exacerbations were defined as those resulting in hospitalization.

The time to first exacerbation (primary efficacy endpoint) was prolonged in both treatment arms. The median time to the first exacerbation could not be determined in the brensocatib-treatment arms due to a low rate of exacerbations and a relatively short trial duration. Instead, the 25th percentile of the time to the first exacerbation was compared among the arms. It was 67 days in the placebo group, 134 days in the 10 mg brensocatib group, and 96 days in the 25 mg brensocatib group with the differences between the placebo and both treatment arms statistically significant ($p = 0.03$ and $p = 0.04$, respectively). The adjusted hazard ratio for brensocatib vs. placebo was 0.58 (95% confidence interval [CI], 0.35 to 0.95) for 10 mg dose and 0.62 (95% CI, 0.38 to 0.99) for the 25 mg dose.

The secondary efficacy endpoints were as follows:

- Rate of exacerbations: 1.37 exacerbations per person-year (95% CI, 1.02 to 1.84) in the placebo group; 0.88 exacerbations per person-year (95% CI, 0.61 to 1.26) in the 10 mg brensocatib group; 1.03 exacerbations per person-year (95% CI, 0.75–1.42) in the 10 mg brensocatib group. Only the difference between the placebo and the 10 mg brensocatib group was statistically significant.
- Change in post-bronchodilator FEV1 percent predicted from baseline: while no significant difference between placebo and the brensocatib groups was detected, a trend in favor of brensocatib was observed. The least-squares mean difference, as compared with placebo, in the percent of the predicted FEV1 was 1.5 percentage points (95% CI, −0.7 to 3.6) in the 10-mg brensocatib group and 1.5 percentage points (95% CI, −0.7 to 3.6) in the 25-mg brensocatib group.
- Change in the Respiratory Symptoms Score (RSS) on the Quality of Life-Bronchiectasis (QoL-B) questionnaire [32] from baseline: while there was numerically greater improvement in the respiratory symptom domain of the QoLB questionnaire among the brensocatib-treated patients, the change did not reach the minimally important difference.
- Change in concentration of active neutrophil elastase in sputum from baseline: during the 24-week treatment period, the mean concentrations of sputum neutrophil elastase were lower in both brensocatib groups than in the placebo group [Figure 1].

A consistent effect of brensocatib was demonstrated in subgroup analyses. For example, the time to first exacerbation was longer, and the annualized rate of exacerbation was lower in brensocatib-treated subjects regardless of age, chronic macrolide therapy, Pseudomonas infection, or presence of peripheral eosinophilia. Geographic region of residence (Europe, North America, Asia-Pacific) had no influence on the outcomes.

The results of phase III randomized placebo-controlled trial of brensocatib in people with non-CF bronchiectasis (ASPEN) trial have recently been [33]. They are discussed below and illustrated in Tables 1–3 and Figures 2 and 3. In this trial, 1767 patients aged 12 to 85 years (1680 adults, 41 adolescents) with history of two or more exacerbations (1 or more exacerbations in adolescents) in the preceding year and whose body mass index (BMI) was ≥18.5 kg/m^2 were randomized to placebo vs. 10 mg vs. 25 mg of brensocatib for 52 weeks. Of note, excluded were patients with a diagnosis of COPD or asthma, if respiratory symptoms were deemed to be primarily driven by these diagnoses (secondary diagnoses were allowed), cystic fibrosis and known or suspected immunodeficiency; current smokers; patients on active treatment for allergic bronchopulmonary aspergillosis, tuberculosis, or non-tuberculous mycobacterial lung disease; patients with chronic use of systemic steroids or immunomodulatory drugs; and patients on supplemental oxygen or with FEV1 <30% predicted.

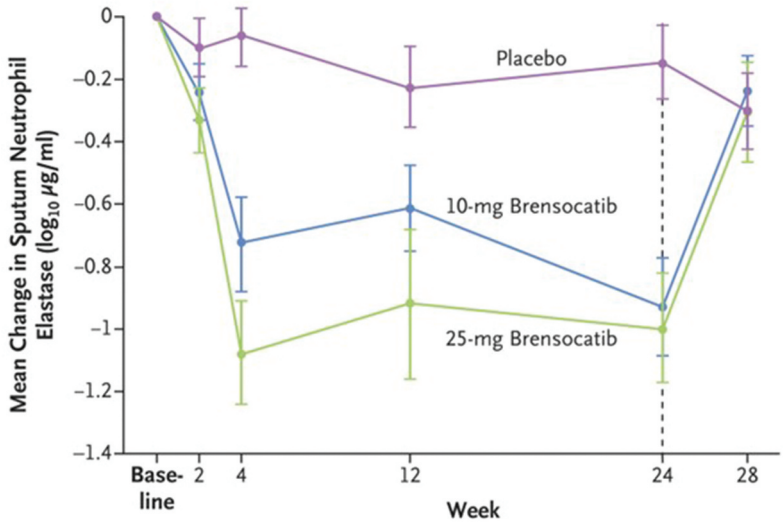

Figure 1. Mean change in sputum neutrophil concentration associated with brensocatib vs. placebo. (From N Engl J Med, Chalmers JD, Haworth CS, Metersky ML, et al. Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis. N Engl J Med 2020;383(22):2127–2137 Copyright © (2025) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society).

Table 1. ASPEN trial. Baseline characteristics [Chalmers, WBC 2024].

	Brensocatib 10 mg (n = 583)	Brensocatib 25 mg (n = 575)	Placebo (*n* = 563)
Age (years), mean ± SD	59.8 ± 15.9	60.6 ± 15.8	60.0 ± 15.4
Age ≥75 years, n (%)	83 (14.2)	84 (14.6)	93 (16.5)
Female sex, n (%)	385 (66.0)	360 (62.6)	362 (64.3)
White race, n (%)	431 (73.9)	430 (74.8)	405 (71.9)
BMI (kg/m^2), mean ± SD	25.5 ± 5.4	25.4 ± 5.1	25.1 ± 4.9
Chronic antibiotic use, n (%)	146 (25.0)	154 (26.8)	133 (23.6)
Macrolides	110 (18.9)	114 (19.8)	105 (18.7)
Use of inhaled steroids, n (%)	324 (55.6)	324 (56.3)	352 (62.5)
Pseudomonas aeruginosa[a] n (%)	203 (34.8)	205 (35.7)	199 (35.3)
≥3 exacerbations in previous 12 months,[a] n (%)	172 (29.5)	163 (28.3)	167 (29.7)
BSI, mean (SD)	7.1 (3.5)	7.1 (3.6)	7.1 (3.6)
Post-bronchodilator % predicted FEV_1, mean (SD)	74.3 (23.4)	74.3 (24.6)	71.9 (22.2)
Blood eosinophil count ≥ 300 cells/μL, n (%)	115 (19.7)	111 (19.3)	106 (18.8)
History of COPD, n (%)	77 (13.2)	83 (14.4)	102 (18.1)
History of asthma, n (%)	101 (17.3)	109 (19.0)	111 (19.7)
QOL-B RSS (adults), mean (SD)	59.8 (16.9)	61.9 (17.2)	60.0 (16.8)

The study completion rate was 78%. The average age was 60. More than 60% of patients were female, and over 70% were white. The use of inhaled steroids was common (>50%). More than a third of patients were colonized with *Pseudomonas aeruginosa* and close to a third had three or more exacerbations in the previous 12 months. Mean bronchiectasis severity index (BSI) was 7.1 (moderate). Post-bronchodilator FEV1 was mildly reduced (74% of predicted) (Table 1).

Improvement in the primary efficacy endpoint – the annualized rate of exacerbations (ARoE) – was achieved in both brensocatib treatment arms: 21.1% and 19.4% risk reduction for the 10 mg dose (ARoE: 1.015 events per year; rate ratio vs. placebo: 0.789; 95% CI, 0.68–0.91) and the 25 mg dose (ARoE: 1.036 events per year; rate ratio vs. placebo: 0.806; 95% CI, 0.69–0.93), respectively (placebo ARoE: 1.286) (Figure 2).

Among the secondary outcomes, the following was observed:

- Time to first pulmonary exacerbation was prolonged in 10 mg (HR = 0.81; CI 0.70 to 0.95) and 25 mg (HR = 0.83; CI 0.70 to 0.97), respectively, vs. placebo
- Proportion of patients free of exacerbation was 48.5% in both the 10 mg and 25 mg of brensocatib arms vs. 40% for placebo (p-values of 0.02 and 0.04 respectively)
- Change in FEV1 was significantly smaller (−24 mL vs. −62 mL) in the 25 mg brensocatib arm vs. placebo (p = 0.0054) but not in the 10 mg brensocatib group (−50 mL, p = 0.38) (Figure 3).
- A nominally[1] significant improvement in the QOL-B RSS of 3.8 points was observed for brensocatib 25 mg dose vs. placebo (p = 0.004).
- No statistically significant difference in the annualized rate of severe exacerbations was noted, yet a trend for a 26% reduction for either the 10 mg or the 25 mg dose when compared with placebo (p = 0.13 and 0.10 respectively) was observed.

Table 2. ASPEN trial. Treatment-emergent adverse events.

	Brensocatib 10 mg (n = 582)[b]	Brensocatib 25 mg (n = 574)[b]	Placebo (n = 563)[b]
Any AE, n (%)	452 (77.7)	440 (76.7)	448 (79.6)
Serious AE	101 (17.4)	97 (16.9)	108 (19.2)
Related AE	72 (12.4)	85 (14.8)	73 (13.0)
Serious related AE	0	1 (0.2)	1 (0.2)
AE leading to death	3 (0.5)	4 (0.7)	7 (1.2)
AE leading to treatment discontinuation	25 (4.3)	22 (3.8)	23 (4.1)
AE leading to trial discontinuation	14 (2.4)	16 (2.8)	16 (2.8)
Most common AEs (≥5% of patients[c]), n (%)			
COVID-19	92 (15.8)	120 (20.9)	89 (15.8)
Nasopharyngitis	45 (7.7)	36 (6.3)	43 (7.6)
Cough	41 (7.0)	35 (6.1)	36 (6.4)
Headache	39 (6.7)	49 (8.5)	39 (6.9)

Table 3. ASPEN trial. Treatment-emergent adverse events of special interest [Chalmers, WBC 2024].

	Brensocatib 10 mg (n = 582)[b]	Brensocatib 25 mg (n = 574)[b]	Placebo (n = 563)[b]
AEs of special interest, n (%)	42 (7.2)	56 (9.8)	53 (9.4)
Hyperkeratosis	8 (1.4)	17 (3.0)	4 (0.7)
Periodontitis/ gingivitis	8 (1.4)	12 (2.1)	15 (2.7)
Severe infection	4 (0.7)	7 (1.2)	4 (0.7)
Pneumonia	23 (4.0)	27 (4.7)	33 (5.9)

5. Safety

In a phase I study of brensocatib in healthy volunteers, no serious adverse effects (AE's) were reported [27]. No trends in laboratory studies, ECG, or infection risk were observed. Considering the known symptoms of the congenital DPP1-inhibitor deficiency (Papillon Lefevre Syndrome), adverse events of special interest (AESI) included skin and gingival disturbances. While a few subjects reported mild gingival bleeding, this did not occur spontaneously but was a result of gum probing, and no difference with placebo was observed. One subject receiving placebo and five subjects receiving brensocatib (four of them receiving 40 mg dose), reported skin-related AESI. These included one or more of the following: skin exfoliation, desquamation, fissuring, dryness, and hyperkeratotic patches on feet and/or hands. All the above resolved within days of drug discontinuation. Interestingly, these symptoms developed before neutrophil elastase activity in whole blood was significantly reduced and resolved, while NE activity remained low after drug discontinuation – suggesting that these symptoms were not mediated by NE activity per se.

The frequency of AEs was similar in the phase II (WILLOW) [30] and phase III (ASPEN) [33] trials. In ASPEN trial, the rates of any AEs (77–80%), related AEs (17–19%), and serious related AEs (0–0.2%) were no different between brensocatib (either dose) and placebo. The most common AEs included COVID-19 (16–21%), nasopharyngitis (6–8%), cough (6–7%), and headache (7–9%). The incidence of adverse events of special interest (AESI) – hyperkeratosis, periodontitis/gingivitis, severe infection, and pneumonia – was low and similar in all arms (Table 2). Of note, no significant relationship between brensocatib exposure (AUC) and AESI was detected [30].

6. Regulatory affairs

Brensocatib received Breakthrough Therapy Designation from the FDA and was granted access to the Priority Medicines (PRIME) scheme by the European Medicines Agency for patients with bronchiectasis in 2020 [34]. The company developing it (Insmed®) is applying for FDA approval [34].

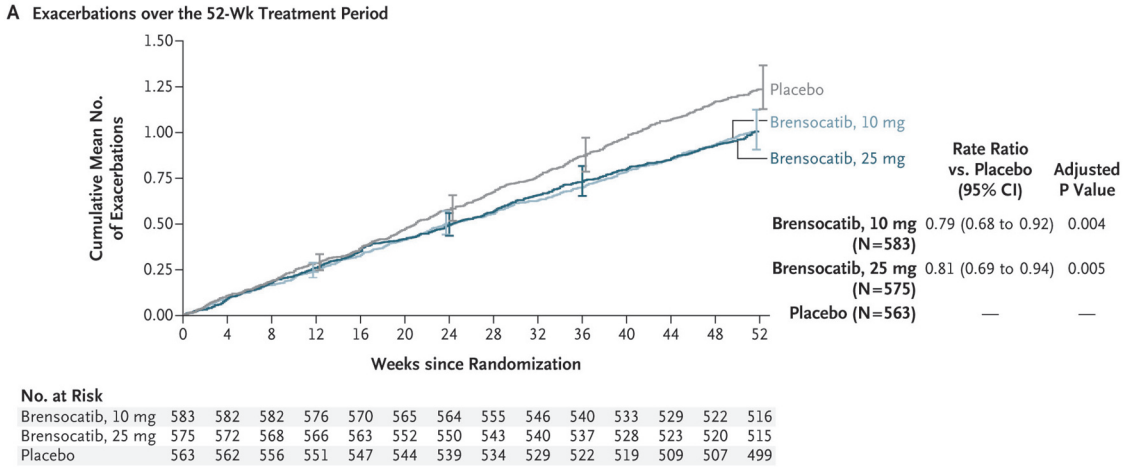

Figure 2. Exacerbations over 52-week period.

(From N Engl J Med., Chalmers JD, Burgel PR, Daley CL, De Soyza A, Haworth CS, Mauger D, Loebinger MR, McShane PJ, Ringshausen FC, Blasi F, Shteinberg M, Mange K, Teper A, Fernandez C, Zambrano M, Fan C, Zhang X, Metersky ML; ASPEN Investigators. Phase 3 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis. N Engl J Med. 2025 Apr 24;392(16):1569–1581. Copyright © (2025) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society).

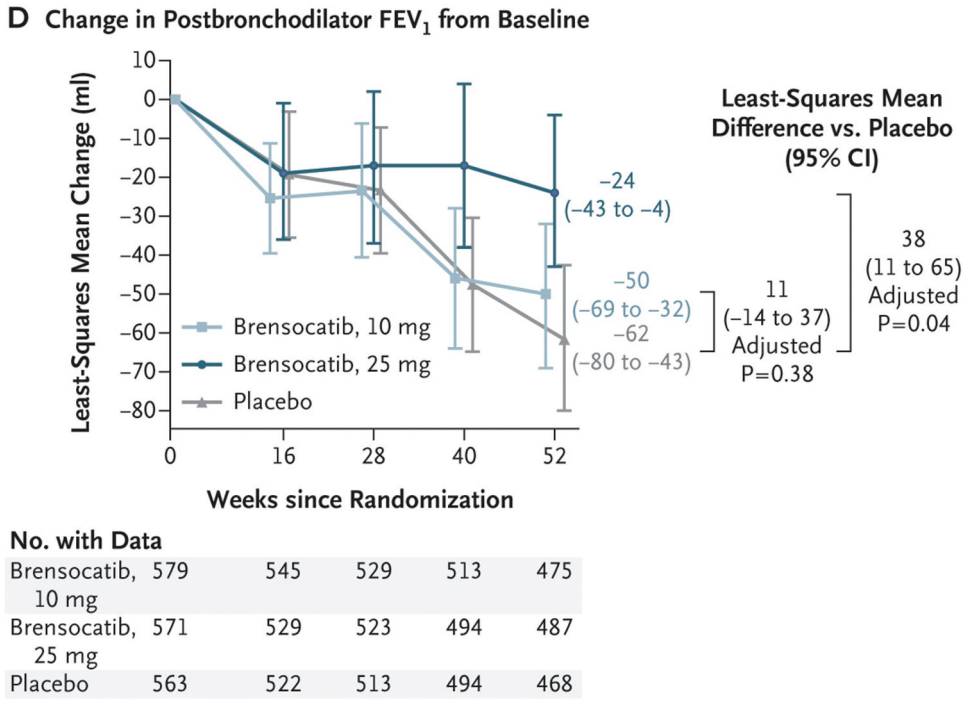

Figure 3. Change in post-bronchodilator FEV1 from baseline.

(From N Engl J Med., Chalmers JD, Burgel PR, Daley CL, De Soyza A, Haworth CS, Mauger D, Loebinger MR, McShane PJ, Ringshausen FC, Blasi F, Shteinberg M, Mange K, Teper A, Fernandez C, Zambrano M, Fan C, Zhang X, Metersky ML; ASPEN Investigators. Phase 3 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis. N Engl J Med. 2025 Apr 24;392(16):1569–1581. Copyright © (2025) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society).

7. Conclusions

Brensocatib is a first-in-class oral reversible inhibitor of DPP1 enzyme that leads to a sustained inhibition of neutrophil serine protease activity in both whole blood and sputum. It is dosed daily, and two doses (10 mg and 25 mg) have been tested in a Phase III clinical trial (ASPEN). This trial has demonstrated clinical effectiveness and safety of brensocatib in bronchiectasis. When administered for 52 weeks, it led to a significant (~20%) reduction in the annualized rate of bronchiectasis exacerbations and improvement in quality of life. The 25 mg dose also significantly reduced the rate of decline in FEV1 compared to placebo, suggesting that there may be a disease modifying effect. The most common adverse effects included nasopharyngitis, headache, and cough at frequencies no different from placebo.

8. Expert opinion

In 2017, a 23-member stakeholder panel including bronchiectasis patients, clinicians, and investigators identified a number of research priorities related to bronchiectasis. Top among them was the need for treatments to (1) prevent exacerbations and (2) improve health-related quality of life [35]. Currently available treatments addressing these needs are limited to inhaled and systemic (predominantly macrolides) antibiotics [21,26].

Brensocatib is the first non-antibiotic, anti-inflammatory (neutrophil-directed) therapy shown to reduce exacerbations and improve quality of life in patients with bronchiectasis. While the absence of comparative effectiveness trials makes it difficult to compare brensocatib to the currently existing treatments, it is notable that in the ASPEN trial, brensocatib reduced the frequency of exacerbations to the same extent (rate ratio 0.79; 95% CI, 0.68–0.91) as that shown for inhaled antibiotics in a recent meta-analysis by Cordeiro et al. (rate ratio 0.78; 95% CI, 0.75–0.96) [21]. Macrolides (particularly azithromycin) may be associated with a greater reduction in the risk of exacerbations (rate ratio 0.49, 95% CI 0.36–0.66) [21,26], but their use is limited by the risk of arrhythmias and antibiotic resistance, particularly among patients with concomitant NTM lung infection (estimated global prevalence of ~10% in patients with bronchiectasis [35]). Furthermore, brensocatib appears to reduce exacerbation rates even in patients on chronic macrolide therapy [33].

Bronchiectasis severity is an important determinant of disease prognosis. Low FEV1 and exacerbation frequency are among several accepted measures of bronchiectasis disease severity that comprise the bronchiectasis severity index (BSI) [36] Disease severity, however, may reflect either a biologically inactive condition (e.g. end-point of prior infection or inflammation) or an active process (e.g. active inflammation with or without infection) that, if left untreated, will progress to a greater level of severity [37]. Several measures of disease activity have been proposed. Among them is sputum neutrophil elastase (NE) concentration. It is noteworthy that treatment with brensocatib, which inhibits neutrophil elastase activation and secretion, was shown to reduce both the frequency of exacerbations and the rate of pulmonary function (i.e. FEV1) decline in bronchiectasis. This finding lends support to the approach of modulating neutrophilic inflammation as a potentially disease-modifying therapy.

Currently available bronchiectasis treatments facilitate mucociliary clearance and reduce the burden of bacterial airway infection. Anti-inflammatory options are limited to macrolides and inhaled corticosteroids. The latter might be beneficial in patients with eosinophilic inflammation (estimated to be around 20% of total) but increase the risk of nontuberculous mycobacterial lung disease [38]. If approved for use, brensocatib will provide an additional tool to reduce exacerbation rates, improve quality of life, and will be the first treatment demonstrated to slow the decline in lung function in patients with bronchiectasis.

Because of these benefits, and because it is likely to be the first agent that is FDA-approved for patients with bronchiectasis, it is likely that it will be widely used in patients with bronchiectasis severe enough to result in impaired quality of life and/or frequent exacerbations. We see brensocatib as an add-on treatment, as opposed to one that will replace current standard therapies, such as airway clearance, inhaled antibiotics, and even chronic macrolide therapy (due to its probably additive beneficial effect in patients on chronic macrolide therapy). For patients not doing well who are not on chronic macrolide therapy, it is hard to predict whether clinicians will choose to add chronic macrolide therapy vs. brensocatib given considerations such as the risks associated with macrolide therapy, the relative effect size of the reduction in exacerbations (larger for macrolide therapy based on currently available data), likely FDA approval for brensocatib but not chronic macrolide therapy and the far greater cost likely for brensocatib than macrolides.

Important gaps in data are whether brensocatib has benefit in patients who have less than two exacerbations yearly, and other patients with relatively common causes of bronchiectasis such as COPD, asthma, and immunosuppression, all of whom were excluded from the brensocatib clinical trials. Longer term safety data and data on lung function decline would also be of interest.

Further into the future, there may be two additional DPP1 inhibitors available, as both the Boehringer and the Haisco Pharmaceutical/Chiesi Farmaceutici DPP1 candidates (BI 1,291,583 and HSK31858 respectively) have reported favorable Phase 2 results [28] and are currently in Phase 3 trials. The frequency with which either of these potential alternatives to brensocatib would be used (if approved) would likely depend on the effect size of improved outcomes and cost, which could influence formulary decisions.

9. Information resources

For further information on clinical manifestations, diagnosis and management of bronchiectasis, latest research in bronchiectasis as well as additional information on brensocatib, the interested reader is directed to the review articles of interest (*, **) below and the following online resources:

https://www.copdfoundation.org/About-Us/Who-We-Are/Bronchiectasis-and-NTM-360.aspx (last accessed 12/21/24)

https://bronchiectasis.hicservices.dundee.ac.uk/ (last accessed 12/21/24)

https://insmed.com/science/our-pillars/brensocatib/ (last accessed 12/24/21)

Note

1. The ASPEN study had a hierarchical statistical significance design, meaning that the secondary outcomes were arranged hierarchically, and only if a higher-ranking secondary outcome met its significance threshold could the lower-ranking outcomes be considered statistically significant. QoL-B RSS was ranked below FEV1. Because the difference in the change in FEV1 for the 10 mg dose of brensocatib did not reach statistical significance, and even though the change in QoL-B RSS p-value was less than 0.05, this difference was reported as 'nominally' rather than 'statistically' significant.

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