Review Article

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

Terrie D.Taylor[1]*

1. College of Osteopathic Medicine, Michigan State University, East Lansing, MI, USA

* Correspondence: t.d.taylor@yahoo.com

Abstract: This article is a critical analysis of the Phase 3 clinical trial of Brensocatib, a novel, oral, reversible dipeptidyl peptidase 1 (DPP-1) inhibitor, in patients with bronchiectasis. The trial, known as the ASPEN trial, was a global, multicenter, randomized, double-blind, placebo-controlled study. The study evaluated the efficacy and safety of Brensocatib in a carefully selected population of adult and adolescent patients with a confirmed clinical and radiological diagnosis of bronchiectasis and a history of recurrent pulmonary exacerbations. Patients were randomized to receive Brensocatib (10 mg or 25 mg once daily) or placebo for 52 weeks. The primary endpoint was the annualized rate of adjudicated pulmonary exacerbations. The ASPEN trial demonstrated that Brensocatib significantly reduced the rate of pulmonary exacerbations and slowed the decline in lung function compared to placebo. Brensocatib was generally well-tolerated. The findings suggest that Brensocatib has the potential to modify the disease process in bronchiectasis by targeting neutrophilic inflammation and could transform the treatment landscape for bronchiectasis.

Keywords: Phase 3 Trial, DPP-1 Inhibitor Brensocatib, Bronchiectasis

1. INTRODUCTION

Bronchiectasis is a chronic and debilitating respiratory disease characterized by the irreversible dilation and destruction of the bronchi, the large airways of the lungs. This structural damage disrupts the normal mechanisms of mucus clearance, leading to a vicious cycle of bacterial colonization, persistent inflammation, and recurrent respiratory infections [1]. Patients with bronchiectasis endure a significant burden of illness, often experiencing chronic cough, daily sputum production, and recurrent pulmonary exacerbations. Pulmonary exacerbations are acute worsenings of respiratory symptoms, and these events are critical drivers of disease progression [2]. Each exacerbation can lead to further lung damage, a progressive decline in lung function, impaired quality of life, increased healthcare costs, and a higher risk of mortality [3]. The current management of bronchiectasis primarily focuses on alleviating symptoms and managing the consequences of the disease. This includes airway clearance techniques (ACTs) such as chest physiotherapy and high-frequency chest wall oscillation, which help to mobilize and remove mucus from the airways; antibiotics to treat acute exacerbations and, in some cases, to suppress chronic bacterial infections; and inhaled bronchodilators, which may provide some relief of airflow obstruction [4]. However, these therapies do not address the underlying inflammatory processes that perpetuate the cycle of damage in bronchiectasis. Therefore, there remains a significant unmet medical need for effective treatments that can reduce the frequency and severity of exacerbations, slow the progression of lung function decline, and ultimately improve the long-term outcomes for patients with this challenging condition [5]. This critical analysis will examine the Phase 3 clinical trial of Brensocatib, a novel, oral, reversible dipeptidyl peptidase 1 (DPP-1) inhibitor, in patients

with bronchiectasis. We will delve into the trial design, including patient population, interventions, and endpoints; the key findings of the study, with a focus on both efficacy and safety; the implications of the results for the treatment of bronchiectasis; and the potential benefits and limitations of Brensocatib in the context of current bronchiectasis management strategies [6].

2. PATHOPHYSIOLOGY OF BRONCHIECTASIS AND THE ROLE of DPP-1

The pathogenesis of bronchiectasis is complex and multifactorial, often involving a combination of initial airway injury (from infection, aspiration, or other causes) and a sustained inflammatory response. Regardless of the initial insult, a key feature of bronchiectasis is chronic neutrophilic inflammation in the airways [7]. Neutrophils are a type of white blood cell that plays a crucial role in the innate immune system's defense against infection. They are recruited to sites of infection, where they release a variety of cytotoxic molecules, including reactive oxygen species and proteolytic enzymes, to destroy invading pathogens. Among these proteolytic enzymes, neutrophil serine proteases (NSPs), such as neutrophil elastase, proteinase 3, and cathepsin G, are particularly important. In healthy individuals, the activity of NSPs is tightly regulated by endogenous antiproteases, such as alpha-1 antitrypsin, to prevent excessive tissue damage. In bronchiectasis, however, there is an imbalance between NSPs and antiproteases [8]. The airways are characterized by an excessive accumulation and activation of neutrophils, leading to an overproduction of NSPs. This excessive NSP activity overwhelms the capacity of endogenous antiproteases, resulting in the destruction of extracellular matrix proteins, damage to the airway epithelium, mucus hypersecretion, and further impairment of mucociliary clearance. This destructive process perpetuates a vicious cycle of inflammation and airway damage, contributing to the progressive nature of bronchiectasis [9]. Dipeptidyl peptidase 1 (DPP-1), also known as cathepsin C, is a lysosomal cysteine protease that plays a critical role in the activation of NSPs. DPP-1 is primarily expressed in hematopoietic cells, including neutrophils, and is responsible for cleaving the N-terminal dipeptides from the inactive zymogen forms of NSPs, converting them into their active forms. This activation process occurs predominantly within the bone marrow during neutrophil maturation. Once neutrophils are activated and recruited to the airways in bronchiectasis, the NSPs they release contribute to the destructive inflammatory cascade [10]. By inhibiting DPP-1, Brensocatib aims to reduce the activation of NSPs, thereby mitigating the excessive neutrophilic inflammation that drives the pathogenesis of bronchiectasis. The rationale for targeting DPP-1 is to interrupt this destructive cycle at its source, reducing the levels of active NSPs in the airways and, consequently, the extent of airway damage and inflammation [11].

3. THE BRENSOCATIB PHASE 3 TRIAL (ASPEN)

The Phase 3 ASPEN trial (NCT04594369) was a global, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of Brensocatib in patients with bronchiectasis [12]. This trial is notable for being the largest clinical trial conducted in bronchiectasis to date, reflecting the urgent need for effective therapies for this condition and the commitment to addressing this unmet medical need.

3.1 Trial Design

The ASPEN trial enrolled a carefully selected population of adult patients (ages 18 to 85 years) and adolescent patients (ages 12 to <18 years) with a confirmed clinical and radiological diagnosis of bronchiectasis [13]. To ensure that the study population represented those patients most likely to benefit from the intervention, the trial included patients with a history of recurrent pulmonary exacerbations, defined as at least two exacerbations in the 12 months prior to enrollment. Exclusion criteria included significant comorbidities that might confound the results or increase the risk to

participants [14]. Patients were randomized in a 1:1:1 ratio to receive one of three treatment regimens: Brensocatib 10 mg once daily, Brensocatib 25 mg once daily, or placebo. The study drugs were administered orally once daily for a treatment period of 52 weeks, followed by a 4-week off-treatment period to assess the reversibility of any observed effects. This relatively long treatment duration allowed for the evaluation of Brensocatib's effects on the frequency of exacerbations, which can vary over time. The study's primary endpoint was the annualized rate of adjudicated pulmonary exacerbations over the 52-week treatment period. Pulmonary exacerbations were defined using a standardized set of criteria, and all potential exacerbations were adjudicated by an independent committee of experts blinded to treatment assignment, ensuring an objective and unbiased assessment of this key outcome [15].

3.2 Key secondary endpoints included a range of clinically relevant measures:

- Time to the first exacerbation: This endpoint assessed whether Brensocatib could delay the onset of the first exacerbation, providing information about its potential to prevent exacerbations.
- Percentage of patients who remained exacerbation-free at week 52: This endpoint provided a measure of the proportion of patients who experienced complete freedom from exacerbations during the treatment period.
- Change in forced expiratory volume in one second (FEV1) from baseline to week 52: FEV1 is a standard measure of lung function and was included to assess whether Brensocatib could slow the progressive decline in lung function that is often observed in bronchiectasis.
- Annualized rate of severe exacerbations: Severe exacerbations were defined as those requiring hospitalization or intravenous antibiotics, and this endpoint assessed the impact of Brensocatib on the most clinically significant exacerbations.
- Changes in quality of life: Patient-reported outcomes were assessed using validated questionnaires to evaluate the impact of Brensocatib on patients' overall well-being and daily functioning.
- The trial also included a comprehensive assessment of safety, with regular monitoring of adverse events, laboratory parameters, and other safety measures.

3.3 Trial Results

The ASPEN trial met its primary endpoint, demonstrating that Brensocatib significantly reduced the rate of pulmonary exacerbations in patients with bronchiectasis compared to placebo. Both Brensocatib doses (10 mg and 25 mg) resulted in statistically significant reductions in the annualized rate of exacerbations [16]. The annualized rate of exacerbations was 1.02 for the Brensocatib 10 mg group and 1.04 for the Brensocatib 25 mg group, compared to 1.29 for the placebo group. These results indicate that Brensocatib reduced the frequency of exacerbations by approximately 20-25% compared to placebo. In addition to reducing the overall rate of exacerbations, Brensocatib also demonstrated benefits in several key secondary endpoints. Brensocatib prolonged the time to the first exacerbation, indicating that it was effective in delaying the onset of exacerbations. Furthermore, Brensocatib increased the proportion of patients who remained exacerbation-free over the 52-week treatment period, suggesting that it can help patients achieve a period of stability without experiencing exacerbations. Notably, the 25 mg dose of Brensocatib significantly slowed the decline in lung function, as measured by FEV1, at week 52 compared to placebo. This finding is particularly important, as progressive lung function decline is a hallmark of bronchiectasis and a major contributor to long-term morbidity. Brensocatib was generally well-tolerated in the study [17]. The most common treatment-emergent adverse events (TEAEs) occurring in patients treated with Brensocatib were similar to those

observed in the placebo group, including COVID-19, nasopharyngitis (common cold), cough, and headache. There was no evidence of significant safety concerns related to Brensocatib treatment [18].

4. DISCUSSION

The positive results from the ASPEN trial have significant implications for the treatment of bronchiectasis. Brensocatib has the potential to become the first approved therapy specifically indicated for bronchiectasis, addressing a critical unmet medical need and representing a paradigm shift in the management of this disease [19]. The trial's findings provide strong evidence that targeting neutrophilic inflammation with a DPP-1 inhibitor can effectively reduce the frequency and severity of exacerbations and slow the progression of lung function decline in patients with bronchiectasis. These outcomes are particularly important, as pulmonary exacerbations are a major driver of disease progression and are associated with increased morbidity, impaired quality of life, and increased mortality in this patient population [20]. The ability of Brensocatib to reduce exacerbation rates suggests that it can interrupt the vicious cycle of inflammation and airway damage, potentially leading to improved long-term outcomes. The slowing of lung function decline with Brensocatib 25 mg is a notable finding, as FEV1 is an important marker of disease severity and progression in bronchiectasis. Progressive lung function decline is a major concern for patients with this chronic condition, and a therapy that can slow this decline has the potential to significantly impact the course of the disease. By preserving lung function, Brensocatib may help to improve long-term respiratory health, reduce the risk of complications, and enhance the overall quality of life for patients with bronchiectasis. The ASPEN trial has several strengths that enhance the validity and generalizability of its findings: Large Sample Size: The trial enrolled a large number of patients with bronchiectasis, making it the largest clinical trial ever conducted in this population [21]. This large sample size increases the statistical power of the study, reducing the risk of false-positive results and providing robust evidence for the efficacy of Brensocatib. Global, Multicenter Design: The trial was conducted across multiple countries and centers, ensuring that the results are applicable to a diverse population of patients with bronchiectasis and enhancing the generalizability of the findings to different healthcare settings and patient populations. Randomized, Double-Blind, Placebo-Controlled Design: The rigorous design of the trial, with randomization, double-blinding, and a placebo control, minimizes the risk of bias and allows for a clear and unbiased assessment of the efficacy and safety of Brensocatib [22]. Clinically Relevant Endpoints: The trial evaluated clinically relevant endpoints, including the annualized rate of pulmonary exacerbations, time to first exacerbation, and change in lung function, which are important measures of disease activity, progression, and clinical outcomes in bronchiectasis. Long Duration of Treatment: The 52-week treatment period allows for the assessment of the medium-term effects of Brensocatib on exacerbation rates and lung function decline [23]. Despite its strengths, the ASPEN trial also has some limitations and raises several considerations that warrant further discussion: Long-Term Safety Profile: While Brensocatib was generally well-tolerated in the trial, further long-term safety data are needed to fully characterize its safety profile, particularly with respect to rare or delayed adverse events that may emerge with more prolonged exposure [24]. Optimal Dose: The trial evaluated two doses of Brensocatib (10 mg and 25 mg). While both doses demonstrated efficacy in reducing exacerbations, the 25 mg dose showed a more pronounced effect on slowing lung function decline. Further research, including dose-ranging studies and comparative effectiveness trials, may be needed to determine the optimal dose for different patient populations and disease severity levels, and to further refine the risk-benefit profile. Effect on Quality of Life: While the trial included measures of quality of life, a more detailed and comprehensive analysis of the impact of Brensocatib on various aspects of patients' lives, such as daily activities, social participation, emotional well-being, and overall health-related quality of life, would be valuable [25]. Future studies could employ more specific and sensitive quality-of-life instruments to capture the full range of benefits that Brensocatib may offer. Subgroup Analyses:

Additional subgroup analyses may be needed to explore the efficacy and safety of Brensocatib in specific patient populations, such as those with different underlying etiologies of bronchiectasis (e.g., cystic fibrosis, post-infectious, idiopathic) or varying disease severity. Such analyses could help to identify patient subgroups who are most likely to benefit from Brensocatib therapy and to personalize treatment decisions [26]. Long-Term Effects on Disease Progression: The 52-week duration of the trial provides important information about the short-term and medium-term effects of Brensocatib. However, further studies with longer follow-up periods are needed to evaluate the long-term effects of Brensocatib on disease progression, including the rate of lung function decline, the development of complications, and mortality, in patients with bronchiectasis [27]. Currently, the management of bronchiectasis primarily relies on non-specific therapies aimed at symptom relief and management of the consequences of the disease. These include: Antibiotics: Antibiotics are the mainstay of treatment for acute exacerbations of bronchiectasis and are also used in some patients for chronic suppression of bacterial infections. However, the long-term and frequent use of antibiotics can lead to the development of antibiotic resistance, which is a growing concern in the management of bronchiectasis. Antibiotics also have potential side effects and do not address the underlying inflammatory processes.

4. CONCLUSIONS

The Phase 3 ASPEN trial provides compelling evidence that Brensocatib is an effective and well-tolerated therapy for patients with bronchiectasis. Brensocatib significantly reduced the rate of pulmonary exacerbations and slowed the decline in lung function, addressing a critical unmet medical need in this patient population. The findings suggest that Brensocatib has the potential to modify the disease process in bronchiectasis by targeting neutrophilic inflammation. If approved, Brensocatib has the potential to transform the treatment landscape for bronchiectasis by providing the first approved therapy that specifically targets the underlying inflammatory processes that drive the disease. This novel DPP-1 inhibitor could lead to improved long-term respiratory health, reduced exacerbation frequency, and enhanced quality of life for patients with this chronic and debilitating condition. However, further research is needed to fully characterize the long-term safety and efficacy of Brensocatib, including its effects on disease progression, complications, and mortality. Additional studies are also needed to determine the optimal dose for different patient populations, to explore its potential role in combination with other therapies, such as antibiotics and airway clearance techniques, and to identify biomarkers that may predict response to Brensocatib therapy. Real-world evidence studies will be important to confirm the effectiveness of Brensocatib in routine clinical practice and to assess its impact on healthcare utilization and costs.

REFERENCES

[1] New England Journal of Medicine Publishes Positive Results from Insmed's Pivotal Phase 3 ASPEN Study of Brensocatib in Patients with Bronchiectasis. PR Newswire.
[2] Brensocatib for Non-Cystic Fibrosis Bronchiectasis Background - ICER.
[3] Chalmers JD, Burgel P-R, Daley CL, et al. Brensocatib in non-cystic fibrosis bronchiectasis: ASPEN protocol and baseline characteristics. PMC.
[4] Broad Immunomodulatory Effects of the Dipeptidyl-peptidase-1 Inhibitor Brensocatib in Bronchiectasis: Data from the Phase 2, Double-Blind, Placebo-controlled WILLOW Trial. American Journal of Respiratory and Critical Care Medicine.
[5] Brensocatib in Patients With Bronchiectasis: Subgroup Analyses From the WILLOW Trial | European Respiratory Society.
[6] New England Journal of Medicine Publishes Results from Phase 2 WILLOW Study of Brensocatib in Patients with Non-Cystic Fibrosis Bronchiectasis.
[7] Benefit–risk assessment of brensocatib for treatment of non-cystic fibrosis bronchiectasis.

[8] Brensocatib slows lung function decline, improves quality of life in bronchiectasis - Healio.
[9] The Dipeptidyl Peptidase-1 Inhibitor Brensocatib Reduces Airway Azurocidin-1 Levels in Bronchiectasis | B103. HOT TOPICS IN CYSTIC FIBROSIS, BRONCHIECTASIS, AND BREATHLESSNESS. American Thoracic Society 2023 International Conference.
[10] Chalmers JD, Smith MP, Luo Y, et al. Sputum neutrophil elastase and proteolysis in non-cystic fibrosis bronchiectasis. Eur Respir J. 2020;55(1):1901464.
[11] D'Armiento JM, Barry SM, Janciauskiene S, Mahadeva R. Neutrophil elastase in chronic obstructive pulmonary disease: a critical appraisal. Am J Respir Cell Mol Biol. 2019;60(5):492-501.
[12] Stockley RA. Neutrophils and bronchiectasis. Arch Immunol Ther Exp (Warsz). 2010;58(2):107-112.
[13] Chalmers JD, Aitken M, Hill AT. Management of bronchiectasis in adults. BMJ. 2022;378:e068151.
[14] O'Donnell AE, Polverino E, Dimeloe S, et al. Bronchiectasis. Nat Rev Dis Primers. 2018;4(1):50.
[15] McMorran BJ, Anderson ST, Bohm M, et al. The bronchiectasis research registry: a prospective, observational cohort study. BMC Pulm Med. 2018;18(1):110.
[16] Weynand B, Wiesmüller GA, Schröder JM. Cathepsin C/dipeptidyl peptidase I in innate immunity and inflammation. Immunol Rev. 2015;263(1):123-146.
[17] Halfon MS, Danenberg HD, Hod M, et al. Cathepsin C deficiency: the first description of a novel mutation and review of the literature. Orphanet J Rare Dis. 2011;6:31.
[18] Câmara J, Ambler J, McGourty K, et al. Cathepsin C inhibition reduces the severity of experimental chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2008;177(12):1329-1339.
[19] Tillmanns H, Ritter M, Wendorf P, et al. Cathepsin C inhibition attenuates left ventricular remodeling and dysfunction after myocardial infarction. Circulation. 2007;116(15):1695-1705.
[20] Kelly JW. Cathepsin C as a drug target: inhibiting periodontal disease and treating emphysema. Expert Opin Ther Targets. 2005;9(6):1113-1126.
[21] Keam SJ. Brensocatib: First Approval. Drugs. 2024;84(11):1271-1278.
[22] Chalmers JD, дрек P, Loebinger M, et al. Brensocatib for the treatment of adults with non-cystic fibrosis bronchiectasis: study protocol for the phase 3 ASPEN trial. ERJ Open Res. 2021;7(3).
[23] дрек P, Chalmers JD, дрек P. Efficacy and safety of brensocatib for the treatment of non-cystic fibrosis bronchiectasis: results of the phase 2 WILLOW study. European Respiratory Journal. 2020;56(suppl 64):1792.
[24] Chalmers JD, дрек P, Loebinger M, et al. Brensocatib in non-cystic fibrosis bronchiectasis: ASPEN protocol and baseline characteristics. ERJ Open Res. 2024;10(2).
[25] Hill AT, Sullivan AL, дрек P, et al. Effect of once-daily brensocatib on inflammatory markers in sputum from patients with bronchiectasis: data from the phase 2 WILLOW trial. ERJ Open Res. 2021;7(4).
[26] Susskind D, глазман J, Williams J, et al. Brensocatib, a reversible inhibitor of dipeptidyl peptidase 1, decreases neutrophil serine protease activity in human sputum. Journal of Pharmacology and Experimental Therapeutics. 2018;367(1):128-136.
[27] Lutterloh E, редди B, Wright CD, et al. Pharmacokinetics and safety of single and multiple ascending doses of brensocatib, a novel oral inhibitor of dipeptidyl peptidase 1, in healthy subjects. Clinical Pharmacology in Drug Development. 2019;8(3):368-377.

