Brensocatib for Non-Cystic Fibrosis Bronchiectasis: Effectiveness and Value

Draft Evidence Report

JULY 23, 2025

Prepared for

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DATE OF PUBLICATION: July 23, 2025

How to cite this document: Wasfy JH, Kim K, Touchette DR, McKenna A, Richardson M, Herce-Hagiwara B, Kim S, Philips M, Ollendorf D. Brensocatib for Non-Cystic Fibrosis Bronchiectasis: Effectiveness and Value; Draft Evidence Report. Institute for Clinical and Economic Review, July 23, 2025**.** https://icer.org/assessment/ncfb-2025/

Jason H. Wasfy served as the lead author on the report. Avery McKenna and Belén Herce-Hagiwara led the systemic review and authorship of the comparative clinical effectiveness section of this report. Kibum Kim, Daniel R. Touchette, and Sodam Kim developed the cost-effectiveness model and authored the corresponding sections of the report in collaboration with Marina Richardson. Marie Phillips conducted the analysis for the budget impact model. Daniel Ollendorf provided methodologic guidance on the clinical and economic sections. We would like to acknowledge the work of Hao-Hsin Huang, Lilah Khoja, and Lauren Lee who worked on the economic model. We would also like to thank Madeline Booth, Anna Geiger, and Grace Ham for their contributions to this report.

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The funding for this report comes from non-profit foundations, with the largest single funder being the Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers (PBMs), or life science companies. ICER receives approximately 22% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. A complete list of funders and more information on ICER's support, is available on the funding page of the ICER website.

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In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following individuals served as external reviewers of the draft evidence report:

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None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions of the draft report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback.

For a list of stakeholders from who we requested input from, or who have submitted public comments so far, please visit: https://icer.org/wp-content/uploads/2025/04/ICER_NCFB_Stakeholder-List_040925.pdf

Conflict of Interest Disclosures for the Report

Table 1. ICER Staff and External Collaborators Conflict of Interest Disclosures

ICER Staff and External Collaborators	Conflict of Interest
Belén Herce-Hagiwara, BA	No conflicts to disclose.
Kibum Kim, PhD	No conflicts to disclose.
Sodam Kim, PharmD, BBA	No conflicts to disclose.
Avery McKenna, BS	No conflicts to disclose.
Daniel Ollendorf, PhD, MPH	No conflicts to disclose.
Marie Phillips, BA	No conflicts to disclose.
Marina Richardson, PhD, MSc	No conflicts to disclose.
Daniel R. Touchette, PharmD, MA	No conflicts to disclose.
Jason H. Wasfy, MD, MPhil	No conflicts to disclose.

Table 2. Expert Reviewers of the Draft Evidence Report Conflict of Interest Disclosures

Expert Reviewer	Conflict of Interest
Doreen Addrizzo-Harris, MD	Dr. Addrizzo-Harris serves as PI of Insmed clinical trials in Bronchiectasis and NTM.
Paul B. Dieffenbach, MD	No conflicts to disclose.
Amy Leitman	Approximately 60-65% of NTM Info and Research funding is received from health care companies.
Julia F. Slejko, PhD	Dr. Slejko is a steering committee member for the COPD Foundation's COPD360Net and collaborates with this organization on a project funded by PhRMA Foundation. Additionally, Dr. Slejko discloses receiving salary funding from AstraZeneca in the last 36 months for position as Followship Program Director.

Table of Contents

List of Acronyms and Abbreviations Used in this Report

%	Percent
AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
BDR	Bronchodilator
BEST	Bronchiectasis Exacerbation and Symptom Tool
BSI	Bronchiectasis Severity Index
CDR	Clinical Trial Diversity Rating
CE	Cost-effectiveness
COPD	Chronic obstructive pulmonary disease
CI	Confidence interval
CT	Computed tomography
evLYs	Equal value of life years
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in one second
HIDI	Health Distribution Index
HR	Hazard ratio
ITT	Intention to treat
LS	Least Squares
MAC	Mycobacterium avium complex
MCID	Minimal clinically importance difference
mg	Milligram
mL	Milliliter
N	Total number
N/A	Not applicable
NCFB	Non-cystic Fibrosis Bronchiectasis
NR	Not reported
NTM	Nontuberculous mycobacteria
PDUFA	Prescription Drug User Fee Act
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
QoL-B RSS	Quality of Life – Bronchiectasis Respiratory Symptoms Scale
RCT	Randomized controlled trial
SD	Standard deviation
SE	Standard error
TBD	To be determined
TEAE	Treatment-emergent adverse event
US	United States

Executive Summary

Bronchiectasis is a chronic lung disease that affects breathing and coughing. Although patients have different symptoms, many suffer from chronic cough, excess mucus, and exacerbations that may involve worsening of these chronic symptoms along with more acute shortness of breath.[1] Bronchiectasis is characterized by a "vicious vortex" of chronic infection, structural lung changes, inflammation, and deterioration in mucociliary clearance (i.e., the way that the body clears the lung of mucus).[2-4] Bronchiectasis can result in significant negative effects on quality of life due to impaired social and physical functioning related to chronic cough and worsening lung function. Exacerbations occur when symptoms worsen, requiring antibiotics and sometimes hospitalization. The dominant form of bronchiectasis is called non-cystic fibrosis bronchiectasis (NCFB). Although bronchiectasis also occurs among individuals with cystic fibrosis, NCFB is substantially more common and much more heterogeneous in terms of etiology, severity, and prognosis than cystic fibrosis.[5] In the United States, NCFB is relatively common and increasingly recognized. An estimated 350,000 to 500,000 adults in the United States have NCFB, with 70,000 new cases emerging annually. Estimated prevalence is highly dependent on the frequency of radiology scans, since many patients especially with less severe versions are underrecognized and underdiagnosed.[6] Among those correctly diagnosed, there is substantial unmet need and no disease-specific therapies.

In the setting of limited treatment options, there are no clinical guidelines for NCFB in the United States. Clinical guidelines in the United Kingdom and Europe for NCFB are based on generally low-quality evidence. For stable outpatients, regular airway clearance therapy at home after using humidification with saline nebulizers and exercise are recommended. For stable outpatients with three or more exacerbations per year, long-term inhaled or oral antibiotics are recommended. Pulmonary rehabilitation is recommended for individuals who are substantially limited by shortness of breath. [7] Unlike for cystic fibrosis, there are no treatments that are specifically approved for NCFB and there are not yet practice guidelines specific to the United States.

However, a potential first treatment specific to NCFB is being evaluated. Brensocatib (Insmed, Inc.), an oral inhibitor of dipeptidyl peptidase 1 (DPP-1) targets neutrophilic serine proteases that mediate inflammation that is part of the "vicious vortex" of NCFB pathophysiology. Brensocatib was recently evaluated in the Phase III ASPEN trial among patients with NCFB who had experienced at least two exacerbations in the 12 months prior to screening.[8] In the ASPEN trial, 25 mg of brensocatib reduced the annualized rate of pulmonary exacerbations relative to placebo (hazard ratio 0.81, 95% CI, 0.69 to 0.94; adjusted P=0.005). In this 3-arm trial, 10 mg of brensocatib was also associated with a similar reduction in pulmonary exacerbations, although only the 25 mg dose was also associated with a statistically significant but very small reduction in the deterioration of lung function.[8] Brensocatib is currently under consideration by the FDA with a PDUFA date scheduled for August 12, 2025.[9]

Given this reduction in a patient-important endpoint (exacerbations) in a large, rigorous, blinded trial, we have confidence that brensocatib improves health outcomes overall within the trial population. However, the size of the overall benefit may be small. There is high certainty of at least a small net health benefit. Conversely, given the pathology of the "vicious vortex," there are mechanistic reasons to speculate that health benefits might be even larger with more time in follow up. However, despite this encouraging data, some important uncertainties remain. Even within the trial population, there was no therapeutic benefit in subgroups of individuals with more severe symptoms and worse lung function. However, at least some clinically important subgroups including those taking chronic antibiotics and those with *Pseudomonas aeruginosa* colonization had benefit similar to the overall trial population. Although patients have told us that they would welcome the reduction in exacerbations observed in the overall population, they have concerns about daily symptoms outside of exacerbations, including fatigue, as well as burdens and side effects of current therapies. The demonstrated quality of life improvement with brensocatib is small and it is not yet clear if brensocatib will improve other outcomes important to patients. Furthermore, brensocatib may also help patients who have fewer exacerbations than those included in the trial, or reduce the progression to clinical illness for individuals who have radiographic evidence of bronchiectasis but no symptoms. However, brensocatib has not yet been tested in these populations and the FDA has not yet provided guidance on the population that should be considered for treatment. The observed reduction in worsening of lung function with the higher dose of brensocatib raises the mechanistic possibility that there may be even greater benefits in clinical symptoms with longer follow up, as objective measures of lung function may precede symptom improvement. However, this conceptual potential remains unclear and has not yet been evaluated empirically. Nevertheless, we see strong evidence of at least a small net health benefit in a well-designed trial and believe that there is the potential for a larger net health benefit over time. We therefore assigned a rating of "B+" ("moderate certainty of a small or substantial net health benefit, with high certainty of at least a comparable net health benefit").

Table ES1. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adolescents and Adults with Non-Cystic Fibrosis Bronchiectasis		
Brensocatib + Usual Care	Usual Care alone	B+

There is no price available yet for brensocatib. For the cost-effectiveness analysis, we used a placeholder price for brensocatib of $82,000 annually based on the manufacturer's earning call presentation in 2024. Relative to usual care alone, and using the placeholder price, our analysis suggests that brensocatib would not meet commonly used cost-effectiveness thresholds. This finding was consistent across numerous sensitivity and scenario analyses including alternative assumptions for disease trajectory, subgroup effects, and additional clinical improvements.

Table ES2. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained	Cost per Exacerbation Avoided
Brensocatib + Usual Care	**Usual Care**	$7,500,000	$7,100,000	$19,100,000	$347,000

evLYs: equal value of life years gained, QALY: quality-adjusted life year

1. Background

Bronchiectasis is a chronic, progressive lung disease that affects breathing and coughing. Many patients have chronic daily cough, excess mucus, and exacerbations that may involve worsening of these chronic symptoms along with shortness of breath, worsening fatigue, and worsening lung function.[1] Bronchi, the small tubes that bring air to the lungs, often become enlarged and colonized with bacteria. Bronchiectasis is characterized by a "vicious cycle" of chronic infection, structural lung changes, inflammation, and deterioration in mucociliary clearance (i.e., the way that the body clears the lung of mucus).[2,3] Given the complexity and synergy between these processes, some have proposed calling such an interaction a "vicious vortex."[4] The coughing and mucus production make bronchiectasis similar to chronic obstructive pulmonary disease (COPD). However, unlike COPD, bronchiectasis is a disorder of the bronchi enlarging.[10] and more often affects the larger airways than COPD..{Hurst, 2015, 5} and more often affects the larger airways than COPD. In bronchiectasis, the enlargement of the bronchi can be seen on computed tomography (CT) scans of the lungs. The diagnosis of bronchiectasis as a clinical syndrome also requires the appearance of typical symptoms related to breathing and coughing. Bronchiectasis can result in significant negative effects on quality of life due to impaired social and physical functioning related to chronic cough and worsening lung function. Bronchiectasis is common among individuals with cystic fibrosis, a relatively rare condition. However, evidence has emerged that in some cases, the type of bronchiectasis that occurs with cystic fibrosis responds to different treatments than other types of bronchiectasis. In that context, bronchiectasis is often called non-cystic fibrosis bronchiectasis (NCFB).[5] This review focuses on the larger population of individuals with NCFB.

In the United States, NCFB is relatively common and increasingly recognized. An estimated 350,000 to 500,000 adults in the United States have NCFB, with 70,000 new cases emerging annually.[6].{Weycker, 2017, 6} There is substantial uncertainty given delayed and missed diagnosis. Older estimates previously suggested lower prevalence.[11,12] The increasing measured prevalence may reflect an actual increase in age-adjusted prevalence of NCFB, an aging population, and/or increased detection, particularly with higher use of high-resolution CT scans. The prevalence increases substantially with age, with large increases starting around age 45. Individuals with NCFB are often misdiagnosed with other conditions, such as COPD. More proactive CT scan imaging can often clarify that NCFB is the underlying cause of symptoms.[6] The annual cost of NCFB care in the United States exceeds $14 billion per year, about $2 billion of which is for hospitalization alone. Other important contributions to cost include laboratory testing, post-acute services, medical equipment, and outpatient care. Adjusted for population size, the cost of NCFB care in the United States is two to three times greater than in comparable countries.[13]

Among those with NCFB in the United States, about two-thirds have at least one exacerbation defined as either an inpatient admitting claims code for NCFB or short-term outpatient antibiotic prescription per year and about one-third have three or more exacerbations per year. Just under half have an exacerbation that requires either intravenous antibiotics and/or inpatient hospitalization.[14] Risk markers for prognosis in bronchiectasis include prior hospitalizations and exacerbations, severity of shortness of breath, lower forced expiratory volume (FEV) in one second (amount of air the lung can force out in one second), colonization with bacteria (including the very resistant *Pseudomonas aeruginosa* and nontuberculous mycobacteria [NTM] such as *Mycobacterium avium*), the number of parts of the lung involved, age, and body-mass index.[15] Bronchiectasis can be caused by a prior lung infection, entry of food or liquid into the lung, inherited genetic disorders, structural disorders of the windpipe, problems with the immune system, and other conditions; in many cases, however, a specific cause cannot be found.[1]

Clinical guidelines for NCFB are based on generally low-quality evidence and interventions are directed at different components of the "vicious vortex." For stable outpatients, regular airway clearance therapy at home is recommended using exercise and one or more of the following techniques: saline nebulizers, high frequency chest wall oscillators (HFCWO), and chest physical and percussion therapy. In patients requiring combination regimens, these therapies can take hours, require substantial effort and planning, and restrict daily activities, work, and travel. after using saline nebulizers, high frequency chest wall oscillators (HFCWO), chest physical and percussion therapy, and exercise are recommended. These therapies can take hours, require substantial effort and planning, and restrict daily activities, work, and travel. For stable outpatients with three or more exacerbations per year, long-term inhaled and oral antibiotics are recommended. These prolonged antibiotic courses can increase the risk of antimicrobial resistance, both for individuals with NCFB and larger populations. Pulmonary rehabilitation is recommended for individuals who are substantially limited by shortness of breath. In some severe cases, surgical resection of part of the lung or even lung transplantation is sometimes considered.[7] Unlike for cystic fibrosis, there are no treatments that are specifically approved for NCFB and there are not yet practice guidelines specific to the United States. As such, there is a substantial unmet need for patients with NCFB.

Brensocatib (Insmed Incorporated) is a small molecule reversible inhibitor of dipeptidyl peptidase 1 (DPP1) that reduces signaling of neutrophils, which is thought to reduce the inflammation that is one of the drivers of the "vicious vortex." The drug is delivered once daily via oral tablet. The manufacturer has announced the submission of a new drug application with the US Food and Drug Administration (FDA), with a decision expected August 12, 2025.[9]

Table 1.1. Interventions of Interest

Intervention	Mechanism of Action	Delivery Route	Prescribing Information
Brensocatib	Dipeptidyl peptidase 1 (DPP1) inhibitor	Daily oral tablet	TBD

mg: milligrams, TBD: to be determined

2. Patient Community Insights

ICER spoke with patients, representatives from the COPD Foundation working as The Bronchiectasis and NTM Association and the NTM Information and Research Organization (NTMir), and several clinical experts to understand the experience of those living with NCFB. The Bronchiectasis & NTM Association also shared a summary of their recent impact survey results. In addition, both organizations shared the ICER Share Your Story Form with their communities, for which we received 80 responses. There was a diverse array of stories and themes across topics such as impacts on daily life, treatment experience, accessing / affording care, and caregiver impacts that are described below. Additional information on methods and the qualitative and quantitative results of the Share Your Story Form submissions are in Supplement Section B.

Patients and patient advocates highlighted that bronchiectasis affects all aspects of daily life, including physical, social, emotional, and work impacts.

The most bothersome physical symptoms mentioned were persistent cough, fatigue, shortness of breath, difficulty walking, and mucus production, which can lead to exacerbations that require treatment and changes to their daily life. Patients discussed avoiding social events due to fatigue, embarrassment due to chronic cough, or fear of getting sick. Others mentioned that they either are no longer able to travel or travel requires additional planning to ensure they can continue airway clearance treatments.

A common sentiment expressed was frustration in not being able to plan ahead due to the unpredictability of bronchiectasis. Patients discussed experiencing anxiety and feeling overwhelmed due to this unpredictability, often leading to modifying daily activities and / or cancelling plans with family and friends last-minute, resulting in social isolation. Patients also expressed worry about how their condition may progress in the future.

Some patients discussed impacts on work, including having to change jobs to something less physically demanding, missing work, switching to remote work, or stopping work altogether.

One patient shared with us:

> *"My life has been impacted profoundly by bronchiectasis. I no longer travel or attend events with crowds of people. Every decision is made with weighing the health risk factors and allowing time to do lung clearance. I never dreamed that this would be my life in my 'golden years' instead of traveling and spending time with friends and family who don't live nearby."*

Many people living with bronchiectasis also have or previously had bacterial colonization (e.g., *P. aeruginosa*, NTM). Those patients shared that they make drastic changes to their daily life (e.g., avoiding tap water, dust, and other environmental exposure) to avoid exposure to these bacteria. One patient explained that to them, "Bronchiectasis is like standing in the middle of the road – it puts you at risk. NTM feels like getting hit by a car, leading to harsh antibiotics and missing work." We heard that any improvements that could lead to the avoidance of these cascading effects towards bacterial colonization would help alleviate a great burden.

There are currently no disease-specific treatments approved for bronchiectasis and most people expressed frustration with currently available options. Daily airway clearance using high frequency chest wall oscillation vests or nebulizers was mentioned most often. However, these techniques can be time-consuming. Patients mentioned that doing airway clearance two to three times daily and cleaning equipment often takes hours out of their day. Self-care at home was described as an emotionally and physically draining process that forces some to wake up early, shift around schedules, and take time away from family and friends. Additionally, airway clearance can be challenging for those who have difficulties producing sputum.

Antibiotics are a mainstay treatment for flare-ups and exacerbations as well as recommended longer term for some patients. People who have NTM/MAC in addition to bronchiectasis have additional complexities regarding care, including additional antibiotics to treat the mycobacteria. However, the continued use of antibiotics can produce major side effects such as hearing loss and gastrointestinal issues.

Patients highlighted concerns about underdiagnosis and misdiagnosis, which is associated with additional emotional burdens of anger, confusion, frustration, and anxiety.[16] Patients also reported difficulty finding physicians and respiratory therapists with substantial experience in NCFB and frustration explaining their condition to others and connecting with supportive resources, given that NCFB is less well known than other lung disorders.[17] One person shared that:

> *"It took two years for me to get diagnosed properly. I wasted that time not getting the treatment I should have been having to prevent the severe lung damage I suffered."*

Some patients shared that they must be their own advocate and carry the burden of finding specialty care. Due to a lack of specialty care centers, patients often travel far distances to receive care, ranging from a two-hour automobile drive to a flight to a different state.

We heard a wide range of perspectives on costs for bronchiectasis management. While some expressed gratitude that they have good insurance coverage or are able to afford medications, others were discouraged about high costs and how difficult it can be to get treatments covered.

One patient mentioned frustration about hidden costs and uncertainty of insurance coverage:

> *"The most expensive parts of my care are things I do not know are not covered or barely covered by insurance. Lab tests have been extremely expensive where I didn't know I'd be responsible for thousands of dollars not covered by insurance. I also was shocked at my personal expense part of a vest device so I decided not to buy/order that given uncertainties on if it would actually help clear my lungs."*

The patients we spoke to expressed great hope for new treatments that could improve quality of life, reduce symptom burden, and slow disease progression. Other hopes included fewer side effects and treatments that are more convenient and have low costs. Most patients shared wishes for rejoining social events, spending time with family, and rejoining valued activities. A reduction in the burdensome effects of exacerbations, infection, fatigue, and mucus production would lead to these improvements in quality of life. This aligns with published research on patient-important research objectives for NCFB, as improving bronchiectasis treatment and preventing exacerbations were cited as top research priorities by patients.[18]

One patient shared their desire to be able to live life fully:

> *"My hope is to be able to work full time in a career that I love, and to be able to have more energy and be as active as I want to. My hope is to be able to hike again, to be able to not live in fear of a common cold, and to know that I can plan for a long life. Above all, I hope to live a life as normally as possible, without this disease as an extra family member I have to consider before all others. I want to LIVE my life, not just survive it."*

Many patients spoke about receiving support from family and friends. Support was described as help with transportation to appointments, treatments, daily responsibilities, household chores, and emotional support. Other patients discussed their ability to take care of themselves or not yet requiring assistance from others, but most acknowledged that assistance may be needed as their condition progresses.

Patients expressed that their condition has impacted their caregivers' quality of life, social life, and work productivity. One patient shared:

> *"Our plans for traveling are pretty much non-existent. Everyone around feels anxiety in case they might unknowingly have anything that could be contagious. A simple cold becomes a reason to cancel a visit. This disease has very much shrunk my and my husband's world."*

Health Equity Considerations

We heard from both patients and patient advocates that in addition to the costs associated with travelling to find care, most treatments patients use to manage symptoms (e.g., nebulizers, high frequency chest wall oscillation devices) lead to high out-of-pocket costs, which can cause some patients to forego treatment in order to save costs. The substantial burden of at home self-care creates barriers to many jobs for both patients and their loved ones, sometimes resulting in lost potential income. Finally, as a disease that primarily affects older patients, patients with NCFB who are already retired may have limited ability to resume employment to generate additional income to meet out-of-pocket costs.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Scope of Review

We evaluated the clinical effectiveness of brensocatib as an add-on therapy to current usual care versus usual care alone for people with non-cystic fibrosis bronchiectasis (NCFB). Usual care may include antibiotics, mucolytics, pulmonary rehabilitation, and airway clearance devices. We sought and reviewed evidence on patient-important outcomes, including the frequency of pulmonary exacerbations, exacerbation-related hospitalizations, lung function, quality of life, and harms, such as pneumonia and infection. The full protocol for the review is available in Supplement Section D1.

Evidence Base

Evidence informing our review of brensocatib for the treatment of NCFB was derived from the Phase III ASPEN randomized controlled trial (RCT). This evidence was supplemented by data from the Phase II WILLOW trial (see Supplement Section D2). Data sources include peer-reviewed publications, conference presentations, and data submissions from the manufacturer.[8,19-26]

Study Design

ASPEN was a 52-week Phase III multi-national randomized trial that evaluated two doses of brensocatib (10 mg and 25 mg) versus placebo. Adult participants (n=1,680) were randomized 1:1:1 and adolescent participants (n=41) were randomized 2:2:1 to 10 mg brensocatib, 25 mg brensocatib, or placebo.[8]

Eligible participants were between 12 and 85 years of age with a clinical history consistent with symptomatic NCFB confirmed by computed tomographic (CT) scan (e.g., cough, recurrent respiratory infections). Adult participants were required to have a history of at least two pulmonary exacerbations (see definition in key outcomes section below) in the 12 months prior to screening and a body mass index (BMI) of 18.5 kg/m^2 or greater at screening. Adolescent participants were required to have at least one pulmonary exacerbation in the prior 12 months and a body weight greater than 30 kg. Participants had be able to produce sputum during screening, with a history of chronic expectoration of at least three months. Key exclusion criteria included: a primary diagnosis of either COPD or asthma, bronchiectasis due to cystic fibrosis, current smokers, known or suspected immunodeficiency disorder, and current treatment for nontuberculous mycobacteria (NTM) lung infection.[27,28]

Participants were allowed to continue on long-term oral or inhaled antibiotics and inhaled corticosteroids. If prescribed by physicians, short-acting and long-acting beta-agonists and muscarinic antagonists (LABA/LAMAs, SABA/SAMAs), anticholinergic bronchodilators, and PDE4 inhibitors were also allowed during the trial. Participants were also allowed to continue airway clearance treatments (e.g., mucolytics, hypertonic saline, pulmonary rehabilitation). Immunomodulatory agents, continuous high-dose nonsteroidal anti-inflammatory drugs, and chronic systemic steroids were prohibited.[27]

Key Outcomes

The primary outcome of the ASPEN trial was the annualized rate of adjudicated pulmonary exacerbations, defined by having at least three of the following symptoms for at least 48 hours: increased cough, increased sputum volume or consistency changes, increased sputum purulence (yellow/green mucus), increased breathlessness, fatigue, and hemoptysis, resulting in a need for a systemic antibiotic prescription.[20]

Key secondary outcomes included: time to the first exacerbation, the percentage of participants who remained exacerbation-free during the treatment period, change from baseline in post-bronchodilator FEV_1, annualized rate of severe exacerbations (defined by need for intravenous antibiotics and/or hospitalization), and the Quality of Life – Bronchiectasis Respiratory Symptoms score (QoL-B RSS). The Bronchiectasis Exacerbation and Symptoms Tool (BEST), a pre-specified exploratory patient-reported outcome, was also presented.[8] These outcomes are described in further detail in the clinical benefit section and defined in Supplement Section A.

Efficacy outcomes were evaluated in the intention-to-treat (ITT) population. Two participants (one in each brensocatib group) were randomized but did not receive treatment and therefore were included in the ITT analysis but not safety analysis set. Given that two dosage strengths of brensocatib were included in the trial, statistical tests for key outcomes were adjusted for multiplicity. Secondary outcomes were statistically tested in a hierarchy. P-values were no longer reported for a group when the hierarchy was broken (i.e., an outcome was not statistically significant). The results presented in Section 3.2 are presented in the order of the hierarchical test.[8,27]

Baseline Characteristics

Participants in the ASPEN trial were around 60 years of age, predominantly White, and approximately 64% were women. Two-thirds of participants had an idiopathic (or unknown cause) etiology of bronchiectasis. Approximately 35% of participants had a positive *P. aeruginosa* culture status at baseline. The mean Bronchiectasis Severity Index (BSI) score (ranges from 0 to 26 where a higher score is more severe; see full definition in Supplement Section A) at baseline was 7.1 across all groups, indicating moderate bronchiectasis severity. The use of long-term antibiotics was

reported by one-quarter of participants in each group, and the use of inhaled glucocorticoids was reported by 56% of participants in the brensocatib group and 63% in the placebo group.[8] (see Table 3.1.) Approximately half of adult participants were taking long-acting beta-2 agonists (LABAs) and 17% were taking long-acting muscarinic antagonists (LAMAs).[20] Additional baseline and study disposition data are in Supplement Tables D3.2 – 3.3.

Table 3.1. Baseline Characteristics from ASPEN Trial[8]

Baseline Characteristics		ASPEN (N=1721)		
		Brensocatib 10 mg (N=583)	Brensocatib 25 mg (N=575)	Placebo (N=563)
Demographic Characteristics				
Age, Mean (SD), Years		59.8 (15.9)	60.6 (15.8)	60.0 (15.4)
Female, n (%)		385 (66.0)	360 (62.6)	362 (64.3)
Race, n (%)	**White**	431 (73.9)	430 (74.8)	405 (71.9)
	Black/African American	2 (0.3)	5 (0.9)	3 (0.5)
	Asian	63 (10.8)	64 (11.1)	64 (11.4)
Condition Characteristics				
Bronchiectasis Etiology, n (%)	**Idiopathic or other**	331 (56.8)	354 (61.6)	321 (57.0)
	Post-Infective*	173 (29.7)	156 (27.1)	174 (30.9)
BSI Score , mean (SD)		7.1 (3.5)	7.1 (3.6)	7.1 (3.6)
Exacerbations in Prior 12 Months	**2†**	411 (70.5)	412 (71.7)	396 (70.3)
	≥3	172 (29.5)	163 (28.3)	167 (29.7)
Positive *Pseudomonas aeruginosa* Culture Status, n (%)		203 (34.8)	205 (35.7)	199 (35.3)
Post-BDR FEV1 % Predicted‡		74.3 (23.4)	74.3 (24.6)	71.9 (22.2)
Baseline Treatment Use				
Long-term Antibiotics#		146 (25.0)	154 (26.8)	133 (23.6)
Inhaled Glucocorticoids		324 (55.6)	324 (56.3)	352 (62.5)

BSI: bronchiectasis severity index, FEV_1: forced expiratory volume in one second, n: number, N: total number, SD: standard deviation

*Pneumonia, childhood infection

†Adolescents with one exacerbation (eight adolescents in the 10-mg brensocatib group, nine in the 25-mg brensocatib group, and four in the placebo group) were included in this category.

‡Baseline FEV_1 values were not available for eight brensocatib-treated participants (four in 10-mg group, four in 25-mg group)

§e.g., macrolides and inhaled antibiotics

Evaluation of Clinical Trial Diversity

We rated the demographic diversity (race/ethnicity, sex, age) of the participants in the trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[29] The ASPEN trial achieved a "Fair" rating on racial/ethnic diversity and a "Good" rating on representation of male and female sex. No rating on the representation of adults ages 65 years and older was calculated due to a lack of prevalence estimates. See Supplement D1 for full details of CDR methods and results.

3.2. Results

Clinical Benefits

The results described below are from the Phase III ASPEN trial.[8] As the results from the Phase II WILLOW trial were similar, data from this study are described in Supplement Section D2.

Primary Outcome

Annualized Rate of Pulmonary Exacerbation

The annualized rate of exacerbations for the 10 mg, 25 mg, and placebo groups were 1.02, 1.04, and 1.29, respectively. Treatment with brensocatib 10 mg or 25 mg resulted in an approximate 20% decrease in the annualized rate of pulmonary exacerbations versus placebo (10 mg vs placebo rate ratio [RR]: 0.79, p=0.004; 25mg vs placebo RR: 0.81, p=0.005) (see Table 3.2).[8]

Table 3.2. Primary Efficacy Results from ASPEN Trial[8]

Outcome		Brensocatib 10 mg N=583	Brensocatib 25 mg N=575	Placebo N=563
Annualized Rate of Pulmonary Exacerbations	Events per year (95%CI)	1.02 (0.91, 1.13)	1.04 (0.93, 1.16)	1.29 (1.16, 1.43)
	Rate ratio (95%CI); p-value vs. placebo	0.79 (0.68, 0.92); p=0.004	0.81 (0.69, 0.94); p=0.005	Reference

95% CI: 95 percent confidence interval, mg: milligrams, N: total number

Secondary Outcomes

Time to First Exacerbation

The median time to first exacerbation for both brensocatib groups was around 50 weeks compared to 37 weeks for placebo.[23] Participants treated with brensocatib had a statistically significant reduction in the incidence of first exacerbation compared to placebo (10 mg hazard ratio [HR] vs. placebo: 0.81, p=0.02; 25 mg HR vs. placebo: 0.83, p=-0.04) and longer time until the first exacerbation compared to placebo (see Table 3.3).[8]

Participants Who Remained Exacerbation Free

At week 52, 49% of participants remained exacerbation-free in both brensocatib groups compared to 40% in the placebo group. This was statistically significant for each brensocatib group versus placebo (see Table 3.3).[8]

Post-Bronchodilator FEV_1

Baseline post-bronchodilator FEV_1 was only reported as the percentage of predicted value and not absolute values (in milliliters). At baseline, brensocatib-treated participants had a post-bronchodilator FEV_1 of 74.3% of the predicted value compared to 72% for placebo, reflecting mild airflow obstruction. The change from baseline to week 52 in post-bronchodilator FEV_1 was greatest in the placebo group (worsening of -62 mL), followed by brensocatib 10 mg (-50 mL) and brensocatib 25 mg (-24 mL), representing slower decline in FEV_1 in participants who received brensocatib compared to placebo. The differences versus placebo were statistically significant for the high dose group but not the low dose (see Table 3.3).[8] Additional lung function outcomes (i.e. post-bronchodilator FVC) are described in Supplement Section D2.

Severe Exacerbations

The annualized rate of severe exacerbations for both brensocatib groups was 0.14 compared to 0.19 for placebo, with no statistically significant difference for the 25 mg dose and no statistical test applied for the 10 mg dose due to hierarchical testing procedures (see Table 3.3).[8]

Quality of Life-Bronchiectasis Respiratory Symptom Score (QoL-B RSS)

The QoL-B RSS is one of eight domains of the QoL-B measure, which was measured as a secondary outcome in the ASPEN trial. This outcome was only measured in adult participants. All other domains were exploratory outcomes and not reported at the time of this review. [27,30]

At baseline, participants across groups had a mean score of around 60 out of 100, with a higher score indicating fewer symptoms. At week 52, all groups had increases in QoL-B RSS scores. (10 mg: +6.8 points, 25 mg: +8.6 points, placebo: +4.8 points).

Participants in the 10 mg and 25 mg brensocatib groups had a mean difference versus placebo of 2.0 points (95%CI: -0.1, 4.1) and 3.8 points (95%CI: 1.7, 5.9), respectively. These results were not tested for statistical significance and did not reach the proposed minimal clinically important difference (MCID) of a change of eight points versus placebo (see Table 3.3).[8,30].

An additional exploratory quality of life outcome (BEST score) was measured but neither the brensocatib groups reached the proposed MCID of a four-point change versus placebo. These results are described in Supplement Section D2**.**

Table 3.3. Key Secondary Efficacy Results from ASPEN Trial[8]

Outcome		Brensocatib 10 mg N=583	Brensocatib 25 mg N=575	Placebo N=563
Time to First Exacerbation	Hazard ratio (95%CI); p-value	0.81 (0.70, 0.95); p=0.02	0.83 (0.70, 0.97); p=0.04	Reference
Participants Who Remained Exacerbation-Free	n (%) with no exacerbations during treatment period	283 (48.5)	279 (48.5)	227 (40.3)
	Rate ratio (95%CI); p-value	1.20 (1.06, 1.37); p=0.02*	1.18 (1.04, 1.34); p=0.04*	Reference
Post-Bronchodilator FEV_1, mL‡	LS mean CFB (SE) at week 52	-50 (9)	-24 (10)	-62 (9)
	LS mean difference versus placebo (95%CI); p-value	11 (-14, 37) p=0.38	38 (11, 65); p=0.04	Reference
Annualized Rate of Severe Exacerbations	Events per year (95%CI)	0.14 (0.10, 0.18)	0.14 (0.11, 0.18)	0.19 (0.14, 0.24)
	Rate ratio (95%CI); p-value	0.74 (0.51, 1.09); NA†	0.74 (0.52, 1.06); p=0.21	Reference
QoL-B Respiratory Symptom Score‡	LS Mean CFB (SE) at week 52	6.84 (0.77)	8.58 (0.76)	4.81 (0.75)
	LS Mean Difference vs. placebo (95%CI); p-value	2.03 (-0.08, 4.14); NA†	3.77 (1.68, 5.85); NA†	Reference

95%CI: 95 percent confidence interval, CFB: change from baseline, FEV_1: forced expiratory volume in one second, LS: least-squares, mg: milligrams, n: number, N: total number, NA: not applicable, QoL-B: quality of life–bronchiectasis, SE: standard error

*The reported p values are based on the odds ratios from logistic regression, as prespecified in the statistical analysis plan, because these p-values were used in the hierarchical testing.

†Statistical testing for this result was not performed according to the hierarchical testing procedure.

‡Baseline data were covariates so patients without baseline / complete measurements were excluded. See Supplement Table D3.5 for n evaluated.

Other Patient Important Outcomes

We sought evidence on patient important outcomes such as changes in background therapy, fatigue, and exacerbation-related hospitalizations or emergency rooms visits, but data were not available at the time of this review.

Harms

Across all arms of the ASPEN trial, the rate of any treatment-emergent adverse events (TEAEs) was similar at week 52 (10mg: 78%, 25 mg: 77%, placebo: 80%). Serious adverse events were reported in 17% of participants in both brensocatib groups and 19% in the placebo group. Approximately 4% of participants in each study group discontinued treatment due to adverse events (see Table 3.5).[8]

The most commonly reported adverse events were COVID-19, nasopharyngitis, cough, and headache. Adverse events of special interest to our review (e.g., hyperkeratosis, dental events [periodontitis, gingivitis], severe infection, and pneumonia) occurred at low rates across study groups. (see Table 3.4). Although infrequent, 3% of participants in the 25 mg group, 1.4% in the 10 mg group, and less than 1% in the placebo group reported hyperkeratosis events. Nearly all the events of were mild or moderate and resolved during the study. One event led to treatment discontinuation for a participant in the 25 mg group.[8]

There were 14 deaths reported due to adverse events ranging from acute respiratory failure to pneumonia to cardiac arrest. No deaths were considered related to treatment with brensocatib.[8] Similar results were observed in the Phase II WILLOW trial.[19] Additional details on harms for the ASPEN and WILLOW trials can be found in Supplement Section D2 and Supplement Table D3.8.

Table 3.4. Key Harms from ASPEN Trial[8]

	Brensocatib 10 mg N = 582	Brensocatib 25 mg N = 574	Placebo N = 563
Any Adverse Event	452 (77.7)	440 (76.7)	448 (79.6)
Serious Adverse Events	101 (17.4)	97 (16.9)	108 (19.2)
Discontinuation Due to Adverse Events	25 (4.3)	22 (3.8)	23 (4.1)
Death Due to Adverse Events	3 (0.5)	4 (0.7)	7 (1.2)
Commonly Reported Adverse Events			
Cough	41 (7.0)	35 (6.1)	36 (6.4)
COVID-19	92 (15.8)	120 (20.9)	89 (15.8)
Headache	39 (6.7)	49 (8.5)	39 (6.9)
Nasopharyngitis	45 (7.7)	36 (6.3)	43 (7.6)
Adverse Events of Special Interest			
Periodontitis / Gingivitis	8 (1.4)	12 (2.1)	15 (2.7)
Hyperkeratosis	8 (1.4)	17 (3.0)	4 (0.7)
Pneumonia	23 (4.0)	27 (4.7)	33 (5.9)
Severe Infection	4 (0.7)	7 (1.2)	4 (0.7)

AE: adverse event, mg: milligram, N: number, TEAE: treatment-emergent adverse event

Subgroup Analyses and Heterogeneity

We sought evidence of effect modification for subgroups of interest including: sociodemographic factors (e.g., sex, age, race, ethnicity), comorbidities (e.g., asthma, COPD), pulmonary exacerbation rate in the prior 12 months, chronic antibiotic use, chronic macrolide use, *pseudomonas aeruginosa* culture status, NTM status, eosinophil phenotype/endotype, and bronchiectasis severity index score.

The main publication for the ASPEN trial presented data on pre-specified subgroups for annualized exacerbation rate and non-peer reviewed presentations and abstracts presented subgroup data for other secondary outcomes.[8,21,22,24-26]

The ASPEN trial concluded that the results of the subgroup analyses for annualized exacerbation rates were generally consistent with overall estimates for both doses of brensocatib. Some subgroups did not demonstrate a clear difference on annualized exacerbations between brensocatib and placebo, in particular, among individuals with FEV_1 <50%, BSI ≥9, or asthma (see Supplement Table D3.6.). However, the trial was not powered to detect treatment differences in the prespecified subgroups. In addition, there were no interaction p-values reported. Therefore, we did not formally evaluate the credibility of these subgroup analyses. Data on select subgroup analyses are in Supplement Tables D3.6-3.7.

Uncertainty and Controversies

There are several uncertainties and controversies related to brensocatib as described below:

- The pivotal ASPEN trial included adults with at least two exacerbations in the prior year and adolescents with at least one exacerbation in the prior year.[8] Conceptually, given the drug mechanism, brensocatib may be effective for individuals with fewer exacerbations, or even pre-clinical bronchiectasis without the NCFB syndrome. However, we do not have outcomes data to support the use of brensocatib in individuals with less symptom burden or without symptoms. Some clinical experts speculate that given the small treatment benefit in the overall trial, any absolute benefit in less symptomatic or asymptomatic patients could be extremely low.
- Although the ASPEN trial enrolled 41 adolescents under age 18, subgroup analyses specifically in this group are underpowered.[8] Although there is no specific reason to believe that the treatment effect of brensocatib is different among adolescents than adults, we do not have certainty about the efficacy of brensocatib in adolescents or children.
- Within the trial population, there was not a clear difference between brensocatib and placebo among individuals with FEV_1 <50%, BSI ≥9, or asthma. As such, there is some residual uncertainty about the efficacy of brensocatib among more symptomatic patients with more advanced lung damage and/or asthma.
- More than half of patients enrolled in the ASPEN trial were taking inhaled corticosteroids, a practice which is common although generally discouraged by treatment guidelines.
- In general, clinical practice guidelines recommend long-term antibiotics in individuals with NCFB who have three or more exacerbations per year.[3,7] This is a more severely ill group than the ASPEN trial population, as roughly one-quarter of ASPEN patients had previously received long-term antibiotics. Reduction in the use of long-term antibiotics would have many potential benefits, including reducing antibiotic resistance in communities and individuals, reduced side effects for patients, as well as reduced burden for patients in administration at home (especially true for inhaled antibiotics). Patients cited the burdens and consequences of antibiotic use to us as we formulated this report. Whether brensocatib reduces the need for long-term antibiotics remains an important unresolved question. Since the number of exacerbations is related to the clinical recommendation for long-term

antibiotics, and since brensocatib reduces exacerbations, a reduction of long-term antibiotic use with brensocatib seems plausible, at least for some patients.

- Patients cited the substantial burden of airway clearance at home as well as limitations on work and travel related to airway clearance as important problems. Whether brensocatib reduces the need for these treatments and/or allows patients with NCFB more flexibility with work, travel, and social activities remains an important unresolved question.
- Given lack of familiarity among general practitioners and even among pulmonary specialists, as well as symptomatic overlap with other conditions, misdiagnosis and delayed diagnosis are common.[31] Essentially every patient we spoke with related a story of misdiagnosis and then delayed diagnosis. To effectively diagnose NCFB in community settings and deliver brensocatib to patients who are likely to benefit, improvements in diagnosis and care delivery are needed. Misdiagnosis in real-world clinical practice will tend to reduce the population-level effectiveness of any new treatment including brensocatib.
- The conceptual model of the vicious vortex is that inflammation, structural lung changes, chronic infection and deterioration in mucociliary clearance are synergistically harmful. As such, it is possible that brensocatib reducing inflammation may improve these other pathophysiological processes and improve outcomes by larger magnitudes in longer-term follow up. However, this remains uncertain. Of note, in the relatively short follow up seen in the ASPEN trial, the 10 mg dose was not associated with significantly less deterioration in FEV_1 but the 25 mg dose was associated with 38 mL less deterioration in FEV_1 relative to placebo (both groups worsened but the 25 mg brensocatib dose was associated with less worsening). A minimally important clinical difference would be 100-140 mL, or a change of 5-10% in FEV_1 although we do not have information about baseline characteristics of enrolled patients to determine baseline absolute FEV_1.[32,33] The observed difference in absolute reduction in deterioration with brensocatib 25 mg is very small from a clinical perspective and likely not meaningful unless associated with larger changes over time.
- Although patient perspectives certainly suggest that reduction in exacerbations are very important, daily symptoms such as fatigue and side effects of medications even when stable are also important. The effect of brensocatib at reducing these burdens is unclear. The improvement in quality of life as measured by the Quality of Life-Bronchiectasis Respiratory Symptom Scale questionnaire observed in the intervention arms of ASPEN is less than the MCID (8 points) for this patient-reported outcome measure.[30] Similarly, any improvement in symptom changes as reported by the exploratory BEST score between brensocatib and placebo also did not reach a proposed MCID (4 points).[8,34]
- Although there is no obvious signal toward problematic side effects of brensocatib, like many Phase III trials, ASPEN is underpowered to detect rare side effects potentially related to the known immunosuppressive function of brensocatib. This is a particular potential concern given the novel mechanism of the drug (DPP1 inhibition) and should be monitored moving forward.
- More recent estimated prevalence of NCFB is much higher than older estimates, likely because increases in use of high-resolution CT scans are detecting more cases.[6,12] Given this issue, there is likely still under recognition and underdiagnosis. If recognition of NCFB is

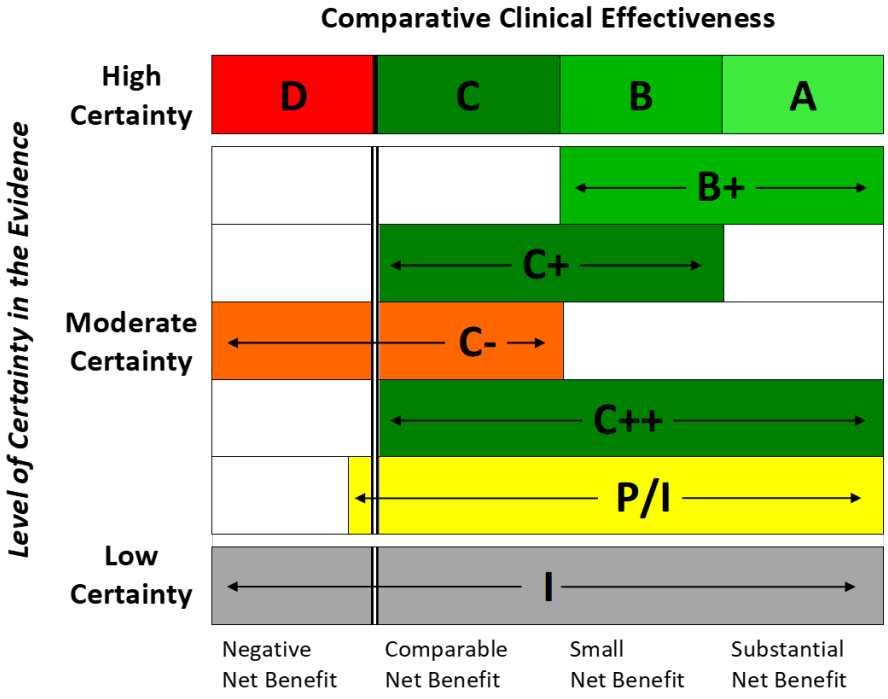
improved, the effectiveness of brensocatib in broader populations, likely with more heterogeneity in type and severity of symptoms, is unclear.

- Current clinical guidelines do not identify any disease-specific treatments for NCFB.[3,7] In general, current guidelines including the role of imaging, diagnostic testing, airway clearance, mucoactive agents, steroids and long-acting bronchodilators, pulmonary rehabilitation, and lung resection surgery and transplantation are based on relatively low levels of evidence. Higher-quality studies including prospective trials on these aspects of treatment would be helpful. Funding for these types of pragmatic comparative effectiveness trials that evaluate many generic therapies remains challenging, however.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" - *High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" - *High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" – *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

The results of the Phase III ASPEN trial demonstrate a difference in annualized pulmonary exacerbations for patients with NCFB who receive brensocatib over and above supportive care alone. Both in our discussions with patients and in published literature, a reduction in the frequency of pulmonary exacerbations was considered to be meaningful. Although the ASPEN trial is statistically underpowered to detect specific side effects of brensocatib, there was no obvious concerning signal of substantial side effects in this relatively large study. Overall, we are encouraged about the evidence for efficacy and safety of brensocatib. We have residual uncertainty, however,

about the efficacy of brensocatib in specific subgroups for since there was no benefit demonstrated in the trial in some subgroups, such as patients with more advanced symptoms and worse baseline lung function (FEV_1 <50% or BSI ≥9).

We also note that there is a substantial burden of disease related to fatigue, daily breathlessness, the burdens of conventional airway clearance, both inhaled and oral antibiotics, and other treatments. Exacerbations are very important to patients but these other outcomes are important as well. While some of these outcomes were measured in the ASPEN trial, they did not differ materially for patients receiving brensocatib relative to placebo. As such, we believe there is evidence for the efficacy of brensocatib while we also note substantial residual burden – particularly of daily symptoms outside of exacerbations – where the effects are less clear. Long-term antibiotics are generally recommended only for individuals with three or more exacerbations per year (a group that represented just over one quarter of the trial population). Reducing the use of long-term antibiotics could have additional benefits both for public health and individual patients, but it remains unclear if brensocatib will reduce the need for these treatments.

We are encouraged to see the evidence of slower deterioration in lung function as measured by FEV_1 although this different is very small in magnitude. Any slower deterioration of lung function may eventually lead to even larger improvements in clinical symptoms, as the "vicious vortex" is interrupted over time. However, this potential has not yet been evaluated clinically and remains speculative, particularly given such a small change in lung function. This leads us to acknowledge at least some potential for even greater benefits than demonstrated in the trial clinically. We see strong evidence for a small net health benefit. Although larger benefits remain speculative, we remain hopeful for the potential of larger benefits with longer follow-up. We are most confident in a small health benefit with brensocatib relative to no disease-specific treatment. Given this, we rate treatment with brensocatib as moderate certainty of a small or substantial net health benefit with high certainty of at least a small net health benefit ("**B+**").

Table 3.4. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adolescents and Adults with Non-Cystic Fibrosis Bronchiectasis		
Brensocatib + Usual Care	Usual Care alone	B+

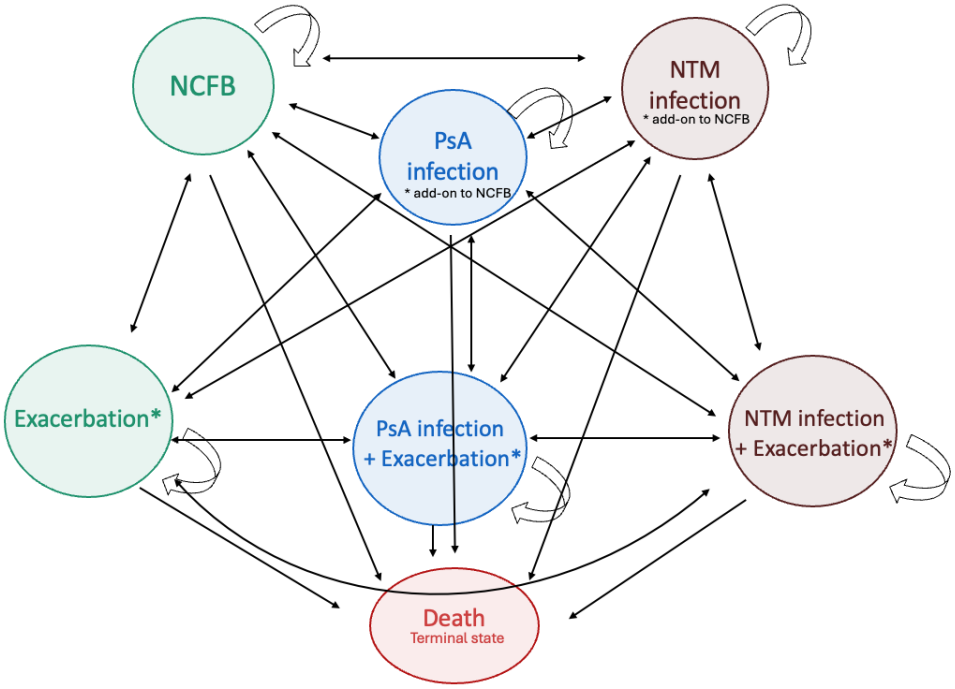
4. Long-Term Cost Effectiveness

4.1. Methods Overview

We developed a *de novo* decision analytic model for this evaluation, informed by key clinical trials and prior relevant economic models.[35-38] Total life years (LY) gained, quality-adjusted life years (QALYs) gained, equal value life years (evLYs) gained, and costs were calculated over a lifetime horizon. As an additional clinical outcome, we assessed the average number of exacerbations avoided per person over the lifetime time horizon. Costs and health outcomes were discounted at 3% per year. The model cycle was one month, to align with clinical data and previously published economic models.[35,37]

The model's hypothetical cohort represented adolescents and adults with NCFB being treated with brensocatib plus usual care ("Brensocatib") compared with usual care alone ("Usual Care"). To align with the pivotal trial, the analytic cohort consisted of patients who had at least two exacerbations in the year prior to beginning treatment with Brensocatib (or Usual Care). Patients remained in the model until death. All patients could transition to the death state due to all-causes or NCFB-specific mortality from any of the alive health states.

Figure 4.1. Model Structure



NCFB: Non-Cystic Fibrosis Bronchiectasis, NTM: Non-Tuberculous Mycobacteria, PsA: Pseudomonas Aeruginosa
*A proportion of individuals having exacerbation will also require hospital admission.
Note. The model structure was based on the heterogeneous clinical presentation of NCFB, incorporating both chronic infection and exacerbation.[4] Given the impact of chronic infection on patient quality of life and healthcare resource utilization, we defined separate health states for those with chronic Pseudomonas aeruginosa (PsA) and chronic nontuberculous mycobacterial (NTM) infections. The model consisted of seven Markov health states: 1) NCFB without exacerbation or chronic infection; 2) NCFB with exacerbation; 3) NCFB with chronic PsA infection without exacerbation; 4) NCFB with chronic PsA infection and exacerbation; 5) NCFB with chronic NTM infection without exacerbation; 6) NCFB with chronic NTM infection and exacerbation; and 7) death. (Figure 4.1).

While the majority of exacerbation episodes can be managed in outpatient settings, a subset of episodes classified as severe exacerbations necessitate hospital admission. The higher costs associated with exacerbation-related hospitalizations were applied to a proportion of patients in the following health states: NCFB with exacerbation; NCFB with chronic PsA infection and exacerbation; and NCFB with chronic NTM infection and exacerbation.

PsA and NTM are two of the most common chronic infections that impact quality of life and increase healthcare costs for patients with NCFB. To account for differences in quality of life and costs for patients with NCFB that also have PsA or NTM infection, separate health states were used in the model (i.e., NCFB + PsA and NCFB + NTM). Patients can transition between these states and to the corresponding exacerbation health states throughout the lifetime horizon.

4.2. Key Model Assumptions and Inputs

Key Model Assumptions

The key model assumptions are presented in Table 1. These assumptions were based on the clinical trial, literature searches, and expert opinion. Additional assumptions can be found in Supplement (Table E2.1).

Table 4.1. Key Model Assumptions

Assumption	Rationale
Model Structure	
The risk of exacerbation is higher in individuals with PsA or NTM infections compared to those with NCFB without chronic infection. However, the risk of the onset of chronic infection and the rate of eradication are assumed to remain consistent across both exacerbated and non-exacerbated states.	Clinical symptoms of NCFB are likely to worsen with chronic infection. Therefore, patients with PsA and NTM have a higher chance of having pulmonary exacerbations. Exacerbation is unlikely to modify the risk of having chronic infection. Currently, there are limited data on how exacerbations influence the onset or eradication of PsA and NTM infections.
Treatment discontinuation from adverse events (AEs) were reflected only in the treatment cost calculation.	Our model used inputs from the intention-to-treat analysis of the ASPEN trial.[8] Thus, the overall treatment efficacy includes patients who both continue and discontinue treatment. Treatment discontinuation decreases the overall pharmacy cost of drug therapy, so the total costs of therapy were adjusted to reflect the proportion of patients who remain on therapy in the clinical trial.
Clinical Efficacy Data	
Brensocatib efficacy data (rate of pulmonary exacerbations) were based on the results from 25 mg once daily arm of the ASPEN trial.	While the primary outcome was similar in both 10 mg and 25 mg doses, we chose the estimates for brensocatib 25 mg because that dose showed statistically significant improvement in forced expiratory volume compared with placebo, while results for the 10 mg dose were not statistically significant.
Adverse events (AEs) only impact treatment discontinuation. No impact of AEs on costs or outcomes were modeled.	The proportion of individuals who experienced adverse events was similar between the treatment and placebo groups. Thus, we did not incorporate AE-related costs or disutilities into the model.
Acute medical attention for an exacerbation would not continue for more than one cycle for most of the patients with exacerbation.	According to expert opinion, most patients receive special attention and care beyond usual care for a week to a month following an exacerbation. After one

Assumption	Rationale
	month, we assumed that usual care with or without brensocatib would suffice for 90% of those with exacerbation.
The proportion of severe exacerbations leading to hospitalization out of all exacerbation is similar between brensocatib and usual care, while the overall rate of pulmonary exacerbations is lower with brensocatib.	Point estimate of the annualized rate of severe exacerbations is lower with brensocatib compared to placebo. However, the confidence intervals for the two groups overlap, which raised concern on uncertainty. For the base-case simulation, we assumed no difference in the proportion of severe exacerbations among all pulmonary exacerbations. The proportion of severe exacerbation lower in the Brensocatib arm was tested in one-way sensitivity analysis.
Costs and Resource Use	
Brensocatib is added-on to usual care.	The proportion of patients requiring usual care—comprising physician visits, antibiotics, mucolytics, and airway clearance—was similar at baseline. Brensocatib demonstrated clinical benefits by reducing the rate of exacerbations. However, brensocatib did not eliminate or reduce the need for ongoing symptom management with usual care while patients remained in the non-exacerbated NCFB state.
Utility	
Multiplicative utility functions were used to calculate some health state utilities	If multiple health attributes are combined into a single health state (e.g. PsA infection and exacerbation), the utility for the health state was calculated as the product of the utilities of individual health attributes.[39]

mg: milligram, MRSA: Methicillin-resistant Staphylococcus aureus, NCFB: Non-Cystic Fibrosis Bronchiectasis, NTM: Non-tuberculous mycobacteria, PsA: Pseudomonas Aeruginosa, QOL-B RSS: Quality of Life-Bronchiectasis Questionnaire Respiratory Symptom Domain Score

Key Model Inputs

Table 4.2 summarizes the key model inputs. These data were based on the clinical trial, literature searches, and expert opinion. Additional inputs can be found in the Supplement (E2. Model Inputs and Assumptions).

Table 4.2. Key Model Inputs

Parameter		Input	Source
Clinical Inputs			
Incidence of Exacerbation (1 Month)*		0.0870	Chalmers, 2025[8]
Risk Ratio for Exacerbation Brensocatib vs Usual Care		0.81	Chalmers, 2025[8]
Proportion of Severe Exacerbation among NCFB Patients with Exacerbations		0.147‡	Chalmers, 2025[8]
Mortality Ratio NCFB with Exacerbation vs NCFB		1.16	Chalmers, 2018[40]
Incidence of PsA Infection per Cycle		0.0025	Aksamit, 2024 [41]
Incidence of NTM Infection per Cycle		0.0034	Aksamit, 2024 [41]
Risk Ratio for PsA or NTM Infection Brensocatib vs Usual Care		0.79†	Chalmers, 2025[8]
Health State Utilities			
NCFB		0.719	Chalmers, 2025[40]
NCFB with Exacerbation		0.545	Chalmers, 2025[40]
NCFB with PsA Infection		0.503	Chalmers, 2014[15]
NCFB with NTM Infection		0.503	Chalmers, 2021; Jiang, 2021; Expert Opinion[42,43]
Severe Exacerbation (Hospital Admission) among NCFB patients with Exacerbations[§]		0.493	Camac, 2021[44]
Costs			
Monthly Cost of Brensocatib		$6,833 ($82,000 annually)[¤]	Insmed Earning Call Q4 2024[45]
Monthly Usual Care Cost	**Outpatient Physician**	$52	Tkacz, 2024[46]
	Pharmacy	$66	
	Other Support	$12	
Cost of Exacerbation	**Outpatient Physician**	$41	
	Pharmacy	$83	
	Acute Care	$885	
Cost of Hospital Admission for Severe Exacerbation		$24,538	Tkacz, 2024[46]
Monthly Cost of Exacerbation, excluding Inpatient Admission		$1,108	Tkacz, 2024[46]
Monthly Cost of PsA Infection[#]		$3,097	Blanchette, 2017[47]
Monthly Cost of NTM Infection[#]		$4,457	Marras, 2018[48]

NCFB: Non-Cystic Fibrosis Bronchiectasis, NTM: Non-tuberculous mycobacteria, PsA: Pseudomonas Aeruginosa, VS: versus

*The 1-month probabilities were calculated from the 1-year probability available from ASPEN trial report

†Derived from the rates of infection or infestation. The overall infection rates of 4.0% for brensocatib 25 mg versus 5.2% for placebo.

‡The proportion and risk ratio of severe exacerbations were derived from annualized rates of severe exacerbations (0.14 for brensocatib 25 mg vs. 0.19 for placebo) relative to annualized rates of all exacerbations (1.04 for brensocatib 25 mg vs. 1.29 for placebo).

§Calculated from COPD exacerbation and hospital admission.
#Costs of PsA infection and NTM infection is not inclusive of exacerbation costs. Costs of exacerbation were applied on top of PsA and NTM infection costs for the exacerbation + chronic infection states.
¤Placeholder price.

Clinical Inputs

The key clinical inputs include transition probabilities calculated from the baseline risk of exacerbation and chronic infection from Usual Care, relative risk of the onset of exacerbation or chronic exacerbation for Brensocatib versus Usual Care, and epidemiology inputs. Clinical inputs were derived from the available literature. The rates of chronic infection and resolution following PsA or NTM infection were extracted from studies that reported these outcomes over extended follow-up periods.[8,41,49] Patient characteristics, as well as the relative risks of exacerbation and infections, were informed by findings from the ASPEN clinical trial.[8] Incidence estimates from the literature were annuitized into monthly cycle inputs with the assumption that the monthly risk would be consistent across the observational period.

Health State Utility Inputs

Health state utilities for each Markov state were calculated from the St George's Respiratory Questionnaire (SGRQ), which is a widely accepted disease specific QoL measure for respiratory conditions including bronchiectasis.[50-53] The Quality of Life-Bronchiectasis questionnaire Respiratory Symptom Domain score (QOL-B RSS) was utilized to measure the patient-reported outcomes for the ASPEN clinical trial.[8] However, due to lack of a converting algorithm from the QOL-B RSS to the EQ-5D, the EQ-5D utility was calculated from SGRQ score using mapping algorithms identified through a targeted review.[54,55] More details about the calculation are available in the Supplement.

Economic Inputs

Since the cost of brensocatib is not yet publicly available, we used a placeholder price based on target pricing information disclosed in the manufacturer's earnings call presentation.

All other cost inputs were derived from a review of the literature and publicly available data sources. Current Usual Care encompasses all direct costs associated with the management of NCFB, including routine physician visits, outpatient medications, and other supportive services. In the event of an exacerbation, additional costs for acute care and outpatient services were added to the baseline costs of non-exacerbation NCFB care. For a subset of exacerbations classified as severe, hospitalization costs were also included to estimate the total direct healthcare costs.[46] Infections with NTM and PsA were assumed to require long-term antibiotic therapy and increased healthcare resource utilization. The associated costs were identified from the literature and annuitized into monthly cost inputs.[47,48] These chronic infection costs were applied in addition to the base NCFB costs once patients transitioned to the corresponding infection state. The costs of chronic infection

were applied in addition to NCFB costs once patients transitioned to the corresponding infection status.

In addition to the direct costs associated with bronchiectasis and related conditions, we incorporated future unrelated healthcare costs. These included the general healthcare costs incurred by the surviving population, irrespective of bronchiectasis management, as well as end-of-life costs.[56] We calculated the age-specific, weighted-average costs of survival for each model cycle, and age-specific, weighted-average costs of death for each mortality event from general population estimates. This approach ensures a more comprehensive estimation of total healthcare expenditures over the modeled time horizon.

4.3. Results

Base-Case Results

We projected costs, QALYs, evLYs, life years gained, and total number of exacerbations for both the Brensocatib and Usual Care arms over a lifetime horizon. Compared to usual care, Brensocatib incurred additional costs, and generates more QALYs, evLYs, and life years. Table 4.3 represents the discounted results for the base case analysis. Incremental cost-effectiveness ratios are presented in table 4.4. All costs were adjusted to December 2024 US dollars.[57]

Table 4.3. Results for the Base Case for Brensocatib Added on to Usual Care Compared to Usual Care

Treatment	Treatment Cost*	Costs, Other Than Treatment	Total Costs†	QALYs	evLYs	Life Years	Number of Exacerbations‡
Brensocatib	$1,103,211	$314,753	$1,417,963	9.32	9.33	13.72	14.69
Usual Care	$20,649	$340,652	$361,301	9.18	9.18	13.67	17.73

evLYs: equal value of life years gained, QALY: quality-adjusted life year

*The cost of brensocatib was estimated using a placeholder price. Treatment costs include brensocatib and Usual Care cost. Life-time discounted costs of brensocatib is $1,082,413 out of $1,103,211 from the brensocatib + Usual Care strategy.

†Total costs include treatment (brensocatib + usual care) and direct medical costs other than the treatment cost

‡Number of exacerbations was discounted at an annual rate of 3%. The undiscounted life-time number of exacerbations for brensocatib and usual care strategies were 20.12 and 24.27, respectively.

Table 4.4. Incremental Cost-Effectiveness Ratios for the Base Case

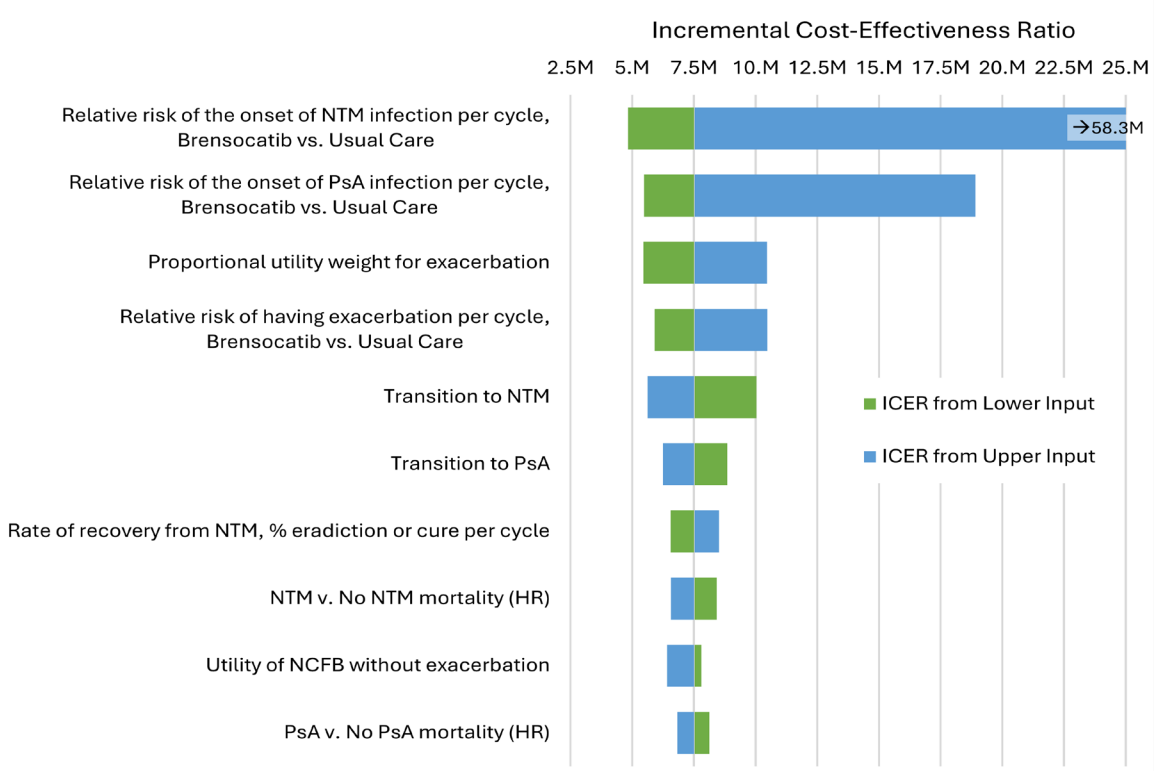
Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained	Cost per Exacerbation Avoided
Brensocatib	**Usual Care**	$7,500,000	$7,100,000	$19,100,000	$347,000

evLYs: equal value of life years gained, QALY: quality-adjusted life year

Sensitivity Analyses

We conducted one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Key drivers that varied the incremental cost-effectiveness ratio were the relative risks of NTM infection, PsA infection, or exacerbation with Brensocatib compared with Usual Care, the proportional utility weight for exacerbation, transition probabilities to PsA infection or NTM infection, rate of recovery from NTM infection, mortality ratio between PsA or NTM infection versus no infection, and utility of NCFB without exacerbation. Figure 4.2 reports the inputs in the order of most influential variables on the incremental cost-effectiveness ratio.

Figure 4.2. Tornado Diagram



NCFB: Non-Cystic Fibrosis Bronchiectasis, NTM: Non-tuberculous mycobacteria, PsA: Pseudomonas Aeruginosa, VS: versus

Probabilistic sensitivity analyses were performed by jointly varying all model parameters over 1,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. Table 4.5 presents the probability of Brensocatib being cost-effective using the thresholds: $50,000, $100,000, $150,000, and $200,000 per QALY or evLY gained.

Table 4.5. Probabilistic Sensitivity Analysis Cost per QALY or evLY Gained Results: Brensocatib + Usual Care versus Usual Care Alone

	Cost Effective at $50,000 per QALY or evLY Gained	Cost Effective at $100,000 per QALY or evLY Gained	Cost Effective at $150,000 per QALY or evLY Gained	Cost Effective at $200,000 per QALY or evLY Gained
Likelihood of Brensocatib Being Cost-Effective	0%	0%	0%	0%

evLYs: equal value of life years gained, QALY: quality-adjusted life year

Additional sensitivity analysis results can be found in the Supplement.

Scenario Analyses

We conducted several scenario analyses, each of which is summarized below.

Analysis 1 (Modified Societal Perspective): A modified societal perspective analysis, including patient productivity losses from absenteeism for inpatient admission and outpatient visit, and sick leave after hospitalization.

Analysis 2 (Impact of Decline in Lung Function): This analysis incorporated the progressive nature of decline in lung function over time and its impact on patient quality of life. FEV1 declines over the lifetime at a rate of 23 ml to 28 ml per year,[58,59] which was calculated from an FEV1 projection algorithm.[60] The FEV1 change was converted to a decrease in the quality of life. We used the following linear association to incorporate lung function change into the model: 100 mL FEV1 gain corresponds to a reduction of 5.9 in SGRQ total score.[61] The SGRQ score was converted to utility weight using a mapping algorithm, calculating decrease in EQ-5D utility from an increase in SGRQ score.[54] The maximum decrease in health utility was capped by 73% of the FEV1-unadjusted utility considering that a severe respiratory disorder could lead to a decrease in the health utility weight by 0.27 of the utility for a mild respiratory disorder.[62]

Analysis 3 (Impact of Brensocatib on a Smaller Decline in Lung Function): This analysis accounted for difference in lung-function changes between Brensocatib and Usual Care and its impact on patient quality of life. In the ASPEN trial, the rate of decline in FEV_1 is slower for brensocatib 25 mg versus placebo.[8] The difference in the loss of lung function would be maintained at the FEV_1 change by the end of the 52-week trial period. The differences in the FEV_1 change between the Brensocatib and Usual Care were converted into EQ-5D utility using the same equation as Scenario Analysis 2.

Analysis 4 (Treatment Effectiveness based on Brensocatib 10 mg): This analysis modeled the clinical trial effectiveness using the results of brensocatib 10 mg compared with placebo from the ASPEN trial.

Analysis 5 (Subgroup analysis by chronic PsA infection): We conducted a subgroup analysis stratified by presence or absence of chronic PsA infection at baseline.

Analysis 6 (Subgroup analysis by number of exacerbations): We conducted a subgroup analysis stratified by the number of exacerbations in the 12 months prior to starting treatment. The number of exacerbations in the prior 12 months was categorized as 2 or ≥3.

Analysis 7 (Impact of time-varying exacerbation rate): The purpose of this scenario analysis was to evaluate the impact of a changing exacerbation rate over time, based on the assumption that patients may have higher chances to experience pulmonary exacerbations as they age. We used annual increases of 2.5% and 5% in exacerbation risk as placeholder inputs for this analysis.

Results from Scenarios are presented in Table 4.6. Detailed scenario analysis results are available in the Supplement.

Table 4.6. Incremental Cost-Effectiveness Ratios for Scenario Analyses

	Cost per QALY Gained	Cost per evLY Gained
Base-Case	$7,514,071	$7,052,553
Scenario 1 (Modified Societal Perspective)	$7,496,808	$7,036,351
Scenario 2 (Impact of Decline in Lung Function)	$8,444,540	$7,343,113
Scenario 3 (Impact of Brensocatib on Decline in Lung Function)	$2,195,677	$2,151,460
Scenario 4 (Treatment Effectiveness based on Brensocatib 10 mg)	$7,373,269	$6,928,809
Scenario 5 (Subgroup Analysis by Chronic PsA Infection)		
PsA+	$8,744,123	$8,148,751
PsA-	$7,543,793	$7,098,588
Scenario 6 (Subgroup Analysis by Number of Exacerbations)		
2 Baseline Exacerbations	$7,067,193	$6,657,921
3+ Baseline Exacerbations	$7,707,425	$7,213,989
Scenario 7 (Impact of Accelerating Exacerbation Rate)		
2.5% increase	$6,923,523	$6,484,747
5% increase	$6,388,708	$5,962,678

evLYs: equal value of life years gained, QALY: quality-adjusted life year

Threshold Analyses

We performed threshold analyses to determine the price needed to meet commonly accepted cost-effectiveness thresholds for QALY and evLY gained ($50,000, $100,000, $150,000, and $200,000 per QALY and evLY gained). The results can be found in Table 4.8 and Table 4.9.

Table 4.7. QALY-Based Threshold Analysis Results

	Anticipated Annual Drug Price*	Annual Drug Price to Achieve $50,000 per QALY Gained	Annual Drug Price to Achieve $100,000 per QALY Gained	Annual Drug Price to Achieve $150,000 per QALY Gained	Annual Drug Price to Achieve $200,000 per QALY Gained
Brensocatib	$82,000	$2,500	$3,000	$3,500	$4,100

QALY: quality-adjusted life year

*A placeholder price from the manufacturer's earning call presentation (Q4 2024)

Table 4.8. evLY-Based Threshold Analysis Results

	Anticipated Annual Drug Price*	Annual Price to Achieve $50,000 per evLY Gained	Annual Price to Achieve $100,000 per evLY Gained	Annual Price to Achieve $150,000 per evLY Gained	Annual Price to Achieve $200,000 per evLY Gained
Brensocatib	$82,000	$2,500	$3,100	$3,700	$4,200

evLYs: equal value of life years gained

*A placeholder price from the manufacturer's earning call presentation (Q4 2024)

Model Validation

We used several approaches to validate the model. First, we provided preliminary model structure, methods and assumptions to manufacturers and patient groups. Based on feedback from these groups, we refined data inputs used in the model, as needed. Second, we varied model input parameters to evaluate face validity of changes in results. Additionally, we performed model verification for model calculations using internal reviewers. As part of ICER's efforts in supporting modeling transparency, we shared the model for external review by the manufacturer around the time of publishing the draft report. Finally, we compared results to other cost-effectiveness models in this therapy area.

The outputs from the model were validated against the trial data for the intervention and also any relevant observational datasets. The total number of exacerbations from our model for the first-year of the treatment was 1.07 and 1.30 for Brensocatib and Usual Care alone, respectively. The projected number of exacerbations were similar to the annualized rate from the clinical trial (1.04 [0.93 to 1.16] for brensocatib 25mg and 1.29 [1.16 to 1.43] and within the 95% confidence intervals.[8] Nominal differences between the model outputs and clinical trials on the annual rate of exacerbation may be attributable to the rate of chronic infection and recovery that we identified from a literature review, due to the lack of input value from the clinical trial. In a follow-up analysis we tested the influence of replacing the exacerbation rate inputs with 0.091 for brensocatib and 0.107 for Usual Care, respectively, calculating the number of exacerbations over the first year matched with the clinical trial data. This input value replacement did not alter the ICER nor changed conclusion. In summary, our model results closely matched findings from the clinical trial.

We also compared the simulated mortality with the anticipated life expectancy among patients with chronic pulmonary conditions. According to the 2025 Trustees Report and US Social Security, the remaining life expectancy of 60 year-old males and females is 21.08 and 24.12 years, respectively,[63] which calculate the weighted average of 23 years. Our modeling approach produced estimates of undiscounted life-expectancy of 18.8 years for brensocatib and 18.7 years for the Usual Care strategy, which is 4.2 to 4.3 years shorter than the general-population life expectancy. Considering that individuals with Stage 2 COPD (moderate COPD with FEV1 50%-79%) and stage 3 COPD (emphysema/chronic bronchitis) have been found to have a 2.2 to 5.8 year reduction in life-expectancy compared to the general population, the modeled life-expectancy for patients in our model appears reasonable.[64,65]

Uncertainty and Controversies

This analysis includes several uncertainties. First, the clinical benefits of brensocatib may involve various underlying mechanisms that are not yet fully understood, limiting the capacity of our model in projecting future outcomes. For instance, brensocatib appeared to delay the downward trajectory of FEV_1, which could represent an additive clinical benefit beyond its impact on exacerbations, or it might be solely mediated by the reduction in exacerbation frequency. Given that loss of FEV_1 with the use of brensocatib 25 mg was less than the FEV_1 loss among those in the usual care group, lung function changes over a patient's lifetime could potentially further impact risk for exacerbations, chronic infections, and patient quality of life. In part to address this uncertainty, we extended the differential FEV_1 change between brensocatib 10mg and 25mg observed during the clinical trial over the patient's lifetime and evaluated the potential change to quality of life. The differential impact on quality of life made through the FEV_1difference substantially decreases the cost-effectiveness ratio from $7.5 million to $2.1 million per QALY gained. Although this does not have an impact on our final conclusion on the cost-effectiveness of brensocatib compared to usual care alone, the preserved lung function could have an impact on the threshold price. Further studies on the impact of lung function on quality of life change are warranted.

Given the anticipated preference for the dose that showed less worsening in lung function as measured by FEV_1, clinical inputs were identified from the outcomes of brensocatib 25 mg. We performed a scenario analysis using the results from the brensocatib 10 mg arm; however, the final approved dose and indication is unknown at this time. Although we modeled a patient population similar to the ASPEN trial, there could be a possibility that the approved indication targets a somewhat different population, compromising the generalizability of our findings.

Furthermore, uncertainty around disease progression and cost inputs exist. For transition probabilities and epidemiology inputs, we relied on targeted literature reviews and expert opinion. Particularly for transition probabilities representing clinical effectiveness, the source of our data is limited to the ASPEN clinical trial. We utilized the results from a 52-week clinical trial, which is insufficient to address the uncertainty around the transition probabilities in our model for the long-term outcome projection. Similarly, care costs may vary across NCFB patients by the complication or severity, which could be another source of uncertainty. Our model includes background costs of NCFB, exacerbation costs, and specific accounting for NTM and PsA infection that we believe comprehensively captures the medical costs of care for patients with NCFB

There was no direct evidence for health state-specific mortality rates in patients with NCFB. Therefore, mortality was estimated using rate ratios obtained from respiratory conditions other than NCFB. Also, some NTM-related inputs were adapted from PsA infection data based on expert judgment, due to limited NTM-specific evidence.

We conducted a modified societal perspective analysis that included indirect costs for patient productivity loss. However, this scenario analysis did not account for caregiver disutility or caregiver productivity loss. Based on our conversations with patients, we recognize that lung clearance can impose a burden on caregivers, potentially affecting their productivity. Nonetheless, there is currently insufficient data to discuss the differential impact on NCFB symptoms between Brensocatib and Usual Care. The observed difference in BEST score between brensocatib and placebo from the ASPEN trial was too small to be meaningfully incorporated into our model. The uncertainty around the impact of brensocatib on the caregiver burden and productivity will need to be addressed as more data become available.

4.4 Summary and Comment

We assessed the cost effectiveness of brensocatib as an add on to usual care compared with usual care alone for patients with NCFB over a lifetime time horizon. Treatment with brensocatib resulted in improvements in quality of life through a reduction in the number of exacerbations and chronic PsA and NTM infections, and higher costs primarily due to the cost of the treatment, compared to usual care alone. At a placeholder price of $82,000 annually, our analysis suggests that brensocatib would not meet commonly used cost-effectiveness thresholds, in either our base case analysis or a number of scenarios based on alternative assumptions around disease trajectory, subgroup affects, or additional clinical improvements.

5. Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention in this review.

Table 5.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
There is substantial unmet need despite currently available treatments.	There are not currently disease-specific therapies for NCFB; in the setting of low evidence, there are not yet clinical practice guidelines specific to the United States. Current therapies that are not specific to NCFB include home treatments such as airway clearance that pose substantial burdens on patients and their caregivers. To inform unmet need as a benefit beyond health, the results for the evLY and QALY absolute and proportional shortfalls have been reported below. evLY shortfalls: • Absolute shortfall: 7.28 • Proportional shortfall: 36.6% QALY shortfalls: • Absolute shortfall: 6.48 • Proportional shortfall: 34.0% The absolute and proportional shortfalls represent the total and proportional health units of remaining quality adjusted life expectancy, respectively, that would be lost due to un- or under-treated illness. Please refer to the ICER Reference Case – Section 2. Quantifying Unmet Need (QALY and evLY Shortfalls) for the shortfalls of other conditions assessed in prior ICER reviews.
This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the healthcare system.	Overall, prevalence estimates in race/ethnic subgroups are difficult to interpret given differential access to care. Known underdiagnosis and misdiagnosis could be even higher in specific populations. Black patients with NCFB have a 53% higher risk of death than White patients with NCFB despite having lower reported exacerbations,

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
	possibly related to socioeconomic factors and/or decreased access to care.[14]
The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.	The home treatments for NCFB can pose substantial burden for caregivers. Brensocatib has the potential to reduce the need for complex home care including airway clearance therapy and nebulizers. These outcomes were not reported in the pivotal trial, so any effect of brensocatib at reducing the need for these other cumbersome therapies is possible but speculative.
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.	As an oral medication, brensocatib may be easier to administer than conventional therapies which include complex care at home that requires specialized equipment. As described above, brensocatib is not an alternative to home care but may reduce the need for home care, but this is speculative based on data currently available.

ICER did not calculate the Health Distribution Index (HIDI) due to a lack of sufficient data on NCFB prevalence in subgroups defined by race and/or ethnicity.

6. Health Benefit Price Benchmark

ICER does not provide a health benefit price benchmark as part of draft reports because results may change with revision following receipt of public comments. We therefore caution readers against assuming that the values provided in the Threshold Prices section of this draft report will match the health benefit price benchmark that will be presented in the next version of this Report.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Results from the cost-effectiveness model were used to estimate the potential total budgetary impact of brensocatib for patients with NCFB. Potential budget impact is defined as the total differential cost of using the new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon. We used the placeholder price for brensocatib of $82,000 annually ($6,833 monthly) and the three threshold prices (at $50,000, $100,000, and $150,000 per evLYG) in our estimates of budget impact.

This potential budget impact analysis included the estimated number of individuals in the US who would be eligible for brensocatib. To estimate the size of the potential candidate population for treatment, we used bronchiectasis prevalence estimates by age group in the US.[6] Applying these estimates to the corresponding size of the US population by age group averaged over the next five years resulted in 461,208 potentially eligible patients.[66] Eligible population estimate calculations are available in Table 7.1. For the purposes of this analysis, we assumed that 20% of these patients would initiate treatment in each of the five years, or 92,242 patients per year.

Table 7.1. Potentially Eligible Population Estimates By Age Group in the US

Age Group	Prevalence of NCFB[6]	Overall US Population[†] by Age Group[66]	Estimated Eligible Population
12-17*	0.007%	24,758,028	1,733
18-34	0.007%	77,207,330	5,405
35-44	0.018%	45,837,321	8,251
45-54	0.043%	40,794,293	17,542
55-64	0.122%	40,369,779	49,251
65-74	0.373%	37,029,359	138,120
75+	0.812%	29,668,417	240,908
Total (12+)	0.156%	295,664,527	461,208

*Adolescent population prevalence assumed to be the same as prevalence for the 18-34 year age group.

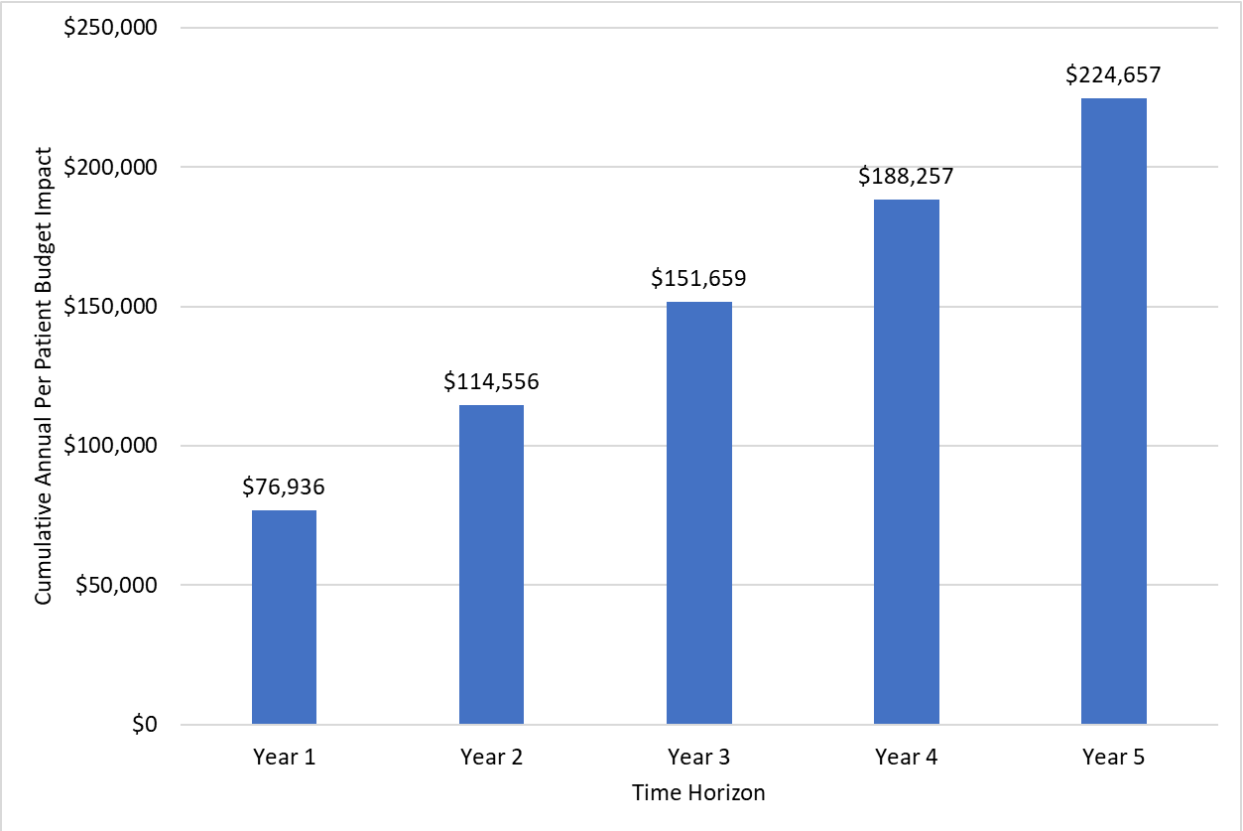
[†]Population estimates averaged over the next five years (2025-2029).

7.2. Results

Figure 7.1 illustrates the cumulative annual per patient treated population budget impact for brensocatib compared to usual care. The cumulative per patient annual budget impact represents the incremental costs of brensocatib compared to usual care across all patients treated within a time horizon (including those who initiated brensocatib in previous years), assuming brensocatib is used with 20% uptake each year over five years.

At brensocatib's placeholder price of $82,000 annually ($6,833 monthly), the average annual budget impact per patient was $76,936 in year one, with cumulative annual budget impact per patient increasing to $224,657 by year five.

Figure 7.1. Cumulative Per Patient Budget Impact for Brensocatib Compared to Usual Care Using a Placeholder Price



Assuming a 20% uptake of brensocatib each year, 3% of patients could be treated over five years at the placeholder price of $82,000 annually before reaching the ICER potential budget impact threshold of $880 million per year. All eligible patients could be treated at the $150,000, $100,000,

and $50,000 per evLYG threshold prices ($3,653, $3,086, and $2,518 annually) before reaching the ICER potential budget impact threshold.

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Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Non-Cystic Fibrosis Bronchiectasis (NCFB): NCFB is a chronic and progressive lung disease characterized by lung damage and inflammation resulting in chronic coughing, mucus production, and recurring lung infection. These symptoms can perpetuate a "vicious vortex" of inflammation, lung damage, infection, and airway dysfunction with worsening of one symptom triggering worsening in any other symptom.[1,3,4]

Pulmonary Exacerbation: Exacerbations in bronchiectasis are generally defined as a sudden worsening of symptoms requiring treatment, usually antibiotics.[7,67] In line with the European Respiratory Society Clinical Research Collaboration (EMBARC) consensus definition for clinical research,[68] the ASPEN trial defined a pulmonary exacerbation as having at least three symptoms (increased cough, increased sputum volume and/or purulence, change in sputum consistency, increased breathlessness and/or decreased exercise tolerance, fatigue and/or malaise, hemoptysis) for at least 48 hours resulting in the prescription of systemic antibiotics.[27]

Severe Pulmonary Exacerbation: The ASPEN trial defined a severe pulmonary exacerbation as one requiring treatment with intravenous (IV) antibiotic drug(s) and/or hospitalization.[69]

Bronchiectasis Severity Index (BSI): The BSI is a validated scoring system of disease severity based on identified predictors of mortality and/or hospitalization: age, body mass index, percent predicted FEV_1, number of hospitalizations in the past two years, frequency of exacerbations in the past 12 months, Medical Research Council Dyspnea Score, colonization with *Pseudomonas aeruginosa* or other organisms, and radiological severity. Scores range from 0 to 26 with a score of 0-4 indicating "mild" disease, a score of 5-8 indicating "moderate" disease, and a score of 9 or above indicating "severe" disease.[15,70]

Quality of Life-Bronchiectasis Questionnaire (QoL-B): The QoL-B is a validated patient-reported outcome measuring symptoms, functioning, and health-related quality of life in individuals with bronchiectasis. The questionnaire consists of 37 items on eight domains (Respiratory Symptoms, Physical Functioning, Role Functioning, Emotional Functioning, Social Functioning, Vitality, Health Perceptions and Treatment Burden). Scores range from 0 to 100 with higher scores indicating better quality of life (e.g. fewer symptoms or better functioning).

- Respiratory Symptom Scale (RSS): This domain of the QoL-B measures symptoms such as congestion, cough sputum production and color, breathlessness, and chest pain. An improvement of 8 points on the Respiratory Symptoms Scale is considered a minimal clinically important difference.[30,71]

Bronchiectasis Exacerbation and Symptom Tool Questionnaire (BEST): The BEST questionnaire is a validated electronic symptom diary measuring daily changes in symptoms (cough, sputum volume and color, shortness of breath, fatigue, and cold and flu symptoms). The tool can be used to detect exacerbations based on changes in symptoms. Scores range from 0 to 26 with higher scores indicating higher symptom burden. A 4-point minimal clinically important difference is proposed.[27,34]

Forced Expiratory Volume in One Second (FEV_1): The volume of air exhaled (in liters) in the first second during forced exhalation after the largest possible inhalation.[72]

Forced Vital Capacity (FVC): The maximal volume of air exhaled (in liters) with a maximally forced effort following full inspiration.[73]

Pseudomonas aeruginosa: *P. aeruginosa* is an opportunistic bacterium commonly found in the environment (e.g., soil, water). It is a common cause of acute or chronic infection in individuals with bronchiectasis. Infection with *P. aeruginosa* has been identified as a risk factor for bronchiectasis severity and disease progression.[74,75]

Nontuberculous mycobacteria (NTM): NTM are a group of bacteria commonly found in the environment (e.g., soil, water). *Mycobacterium* (*M.*) *avium* complex (MAC) is the most common group of NTM. Infection with NTM can be a cause of bronchiectasis or bronchiectasis can be a risk factor for developing an infection with NTM.[76]

Other Relevant Definitions

Absolute and Proportional Shortfalls: Absolute and proportional shortfalls are empirical measurements that capture different aspects of society's instincts for prioritization related to the severity or burden of an illness. The absolute shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[77] The ethical consequences of using absolute shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute shortfall. The proportional shortfall is measured by calculating the proportion of the total health units of remaining life expectancy that would be lost due to untreated illness.[78,79] The proportional shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute shortfall, rapidly fatal conditions of childhood have high proportional shortfalls, but high numbers can also often arise from severe conditions among older adults who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment. Details on how to calculate the absolute and proportional QALY and evLY shortfalls can be found in ICER's reference

case. Shortfalls will be highlighted when asking the independent appraisal committees to vote on unmet need despite current treatment options as part of characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

Health Improvement Distribution Index (HIDI): The HIDI identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The HIDI is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if a disease has a prevalence of 10% among Black Americans whereas the disease prevalence among all Americans is 4%, then the Health Improvement Distribution Index is 10%/4%=2.5. In this example, a HIDI of 2.5 means that Black Americans as a subpopulation would benefit more on a relative basis (2.5 times more) from a new effective intervention compared with the overall population. HIDIs above 1 suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. The HIDI may be helpful in characterizing a treatment's benefits beyond health and special ethical priorities (Section 5). ICER did not calculate the Health Distribution Index (HIDI) due to a lack of sufficient data of NCFB rates in racial and ethnic minority populations.

A2. Potential Cost-Saving Measures in Non-Cystic Fibrosis Bronchiectasis

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by therapies for NCFB (e.g., reduced need for emergency department visits and hospitalizations), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of NCFB beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with NCFB that could be reduced, eliminated, or made more efficient. The manufacturer of brensocatib highlighted the economic burden of exacerbations, which lead to higher all-case and respiratory-related hospitalizations and longer hospital stays.

A3. Patient Input on Clinical Trial Design

We solicited this information from the manufacturer of brensocatib. They shared the following: "ePRO was used to collect patient-reported outcomes in ASPEN and WILLOW. In general, Insmed collaborates with patient communities early and consistently throughout our clinical development programs to capture what matters most to patients, with an aim towards improving the care and experiences of people living with serious diseases."

B. Patient Community Insights: Supplemental Information

B1. Methods

We spoke with and received feedback from patients, caregivers, and patient advocacy organizations. The COPD Foundation doing business as The Bronchiectasis and NTM Association and NTM Information and Research (NTMir) organization provided information and resources as well as connected us with people living with bronchiectasis for discussions. We spoke with six people who provided varying perspectives on living with bronchiectasis. The Bronchiectasis & NTM Association provided us with results of a bronchiectasis impact survey they conducted. Both organizations shared the ICER Share Your Story Form with their communities.

ICER received a total of 80 responses on the Share Your Story Form. The form included five questions to better understand the experience of living with NCFB, described below:

1. How has your disease/condition affected your day-to-day life (physical, emotional, or otherwise)?
2. What is your experience with previous and/or current treatments?
3. What is your experience with accessing and affording care for your disease/condition?
4. What are your hopes for a new treatment?
5. How has your disease/condition impacted your family and caregivers?

We conducted a qualitative, thematic analysis of this set of responses with the results outlined below.

Insights from the patient organizations, patient discussions, and survey responses directly informed the patient community insights section of our report (see Section 2).

B2. Results

Survey respondents shared information on some or all of the categories described below. As the questions were open-ended, we recognize responses may not reflect the entirety of someone's experience with bronchiectasis but rather what they felt was most relevant to share. The responses we received show a wide array of perspectives, difficulties, and hopes of people with bronchiectasis. We are grateful to each person who shared their unique story. Based on the questions in the form, we extracted key themes across the responses, supplemented by summary statistics and quotes where applicable.

Participant Type

Of the 80 respondents, 78 identified themselves as patients and two as caregivers.

Condition Type

Of the 78 patients with bronchiectasis, 30 reported having bronchiectasis alone, 42 also reported NTM / MAC, three had *Pseudomonas aeruginosa*, two reported COPD, and three reported other additional comorbid conditions or causes of NCFB (e.g., sarcoidosis, primary ciliary dyskinesia).

Condition Type*	n (%)
Bronchiectasis	30 (37.5)
Bronchiectasis & NTM / MAC	42 (52.5)
Bronchiectasis & *Pseudomonas aeruginosa*	3 (3.8)
Bronchiectasis & COPD	2 (2.5)
Bronchiectasis & Other	3 (3.8)

COPD: chronic obstructive pulmonary disease, MAC: mycobacterium avium complex, NTM: non-tuberculous mycobacteria

*Some respondents had multiple conditions (e.g., bronchiectasis with NTM and COPD) so the groups below are not mutually exclusive.

Daily Life Impact

When asked about the daily life impacts of bronchiectasis, responses were categorized within four main categories: social, physical, emotional, work/career impacts.

Social Impacts

Many respondents (48%) mentioned that living with bronchiectasis has impaired their social life. In addition, 18% mentioned that it has impacted their ability to travel.

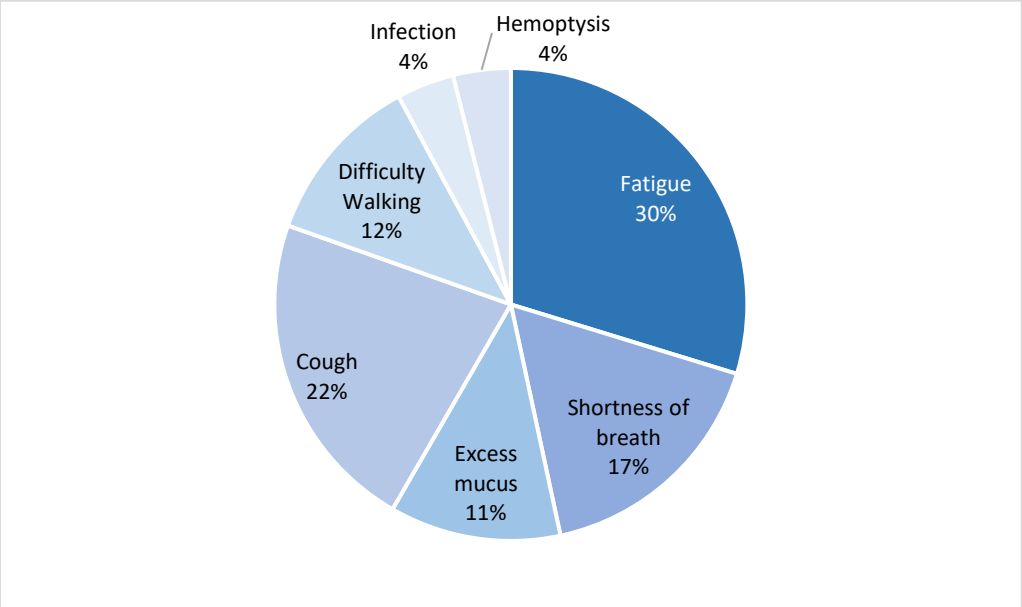
- "The constant rattly mucus cough makes it embarrassing to be with new people. Difficult when eating to have to cough especially with people in a dining facility. Since Covid is even harder because people hear your cough and think you are contagious. I find myself staying away from people too if they have a cough. Very nervous around people in case I pick up a flu bug. Therefore, I don't go out much and avoid anywhere there are people I don't know or gatherings like showers or small parties. I have become recluse."

- "My life has been impacted profoundly by bronchiectasis. I no longer travel or attend events with crowds of people. Every decision is made with weighing the health risk factors and allowing time to do lung clearance.... I never dreamed that this would be my life in my 'golden years' instead of traveling and spending time with friends and family who don't live nearby."

Physical Impacts

The most common physical symptoms reported were fatigue, cough, shortness of breath, excess mucus, and difficulty walking (see Figure B2.1).

Figure B2.1 Most Commonly Mentioned Physical Symptoms



- "Physically, I am becoming slower due to my progressive lung deterioration. I feel that I have been knocked down at the knees, with a one-way sentence to a more and more restrictive lifestyle. I am hoping and praying for a therapy that will help my symptoms."

- "It has completely changed my life. I used to be a marathon runner. I loved exercise and being outside. Now my day is taken up with using a nebulizer air vest and taking medication. I get very tired by the late afternoon and have to lay down. I feel I have aged 10 years in the last six months."

- "Daily life has changed on my condition is the worst. It feels like I can't get any air until I can get some medication into me for some days. I get a brief reprieve of several hours and I feel almost like human otherwise it is demoralizing and the energizing to struggle with this condition."

- "No two days are ever the same and you never really know how you are going to feel from one day to the next. Walking uphill and climbing stairs is still tough. I can walk faster now than I did when I was first diagnosed. I do daily airway clearance and walk when I can."

Emotional Impacts

Nearly half of respondents (44%) commented on how living with bronchiectasis has led them to feel misunderstood, self-conscious, or overwhelmed. Many discussed that it has been difficult to stay positive at times.

- "I'm conscious of my cough and rarely go out to cinema or restaurant because people stare and are naturally afraid I am infectious. I used to love to travel but have to wear masks and try not to cough on flights. Again embarrassment and discomfort."

- "I felt like an older person at the age of 40 and continue to feel as if I am much older than I am. I am a very positive person but my life would have been much different if I did not have to deal with this condition throughout the past years. Chronic disease eventually takes a toll on one's self-esteem."

- "To hear that you have something for which there is no treatment to really stop the progression nor is there a cure is devastating on a level I've never experience before. I went into a deep depression."

Work/Career Impacts

Some people (20%) highlighted impacts on work, including having to stop work, change jobs, miss work, or switch to remote work.

- "I had to leave my career that I loved because I was sick so often and had no energy to work. This disease has affected my whole life and future."

- "I am thankful I work in a clinic that is so supportive otherwise I probably wouldn't be able to work. It seems when I have a flare, they last so long. I can be out of work 4 to 6 weeks. This condition is exhausting."

Experience with Treatment

Type of Treatment

Many people mentioned experience with airway clearance devices such as high frequency chest wall oscillation vests (50%), nebulizers (50%), and antibiotics (39%). Other management strategies mentioned less frequently include exercise, intravenous immunoglobulin (IVIG) infusions, expectorant/decongestant medications (e.g., Mucinex).

Side Effects

Most mentions of side effects were in relation to antibiotics (36%).

- "I have been on 16 different antibiotics, many of them for over a year at a time, and three antibiotics at a time. I have been on airway clearance for 13 years. The biggest side effect is hearing loss. Second is digestive issues."

- "My treatment thus far has mostly centered on prevention of exacerbations through regular lung clearance and taking azithromycin daily. While the azithromycin has definitely helped, it has also caused a dramatic hearing loss which required that I get hearing aids. I do however, still have occasional exacerbations which require me to take doxycycline and prednisone. This protocol helps, but doesn't always totally eliminate the symptoms."

- "Multiple antibiotics take an unseen toll on one's gut microbiome over time. You do not realize the long-term effects until it is often too late. Gastrointestinal dysbiosis from years of antibiotics has also led to bladder wall lesions."

Treatment Limitations

The two limitations discussed most were that current treatments were time-consuming and difficult to administer.

- "With all the morning and evening lung therapy (nebulizers and vest), I have to get up earlier in the mornings, and since I can't do my lung therapy close to when I eat, dinner has to be over by 8:00 PM."

- "It is VERY challenging for me to bring up sputum despite using a nebulizer and handheld breathing devices --that process is very frustrating and affects me emotionally"

- "My routines of nebulizing, drainage and air clearance dictate my day and create problems when traveling or socializing. It's been very draining to my mental and physical well-being."

Experience with Accessing & Affording Care

For this question, 68% of people wrote about affording care and 59% wrote about accessing care.

Affording Care

When asked about difficulties in affording care, people wrote about out-of-pocket costs (36%), high costs (26%), and insurance (24%) the most. As there are no disease-specific treatments approved, some people shared that other therapies they use, such as airway clearance devices and nebulizer equipment, are often not covered by insurance. While some expressed gratitude that they have good insurance coverage or can afford medications, others were discouraged by how difficult it can be to get treatments covered.

- "We incur the travel (airfare) costs as well as whatever portion of the bill that is not covered by Medicare. Any part of my wife's treatment that is considered durable medical equipment (such as the saline nebulizer) seems to have poor coverage. Likewise, the Volara device was an out-of-pocket expense. So in summary, although we have Medicare and a supplement with Anthem Blue Cross, we end up paying out of pocket expenses of up to $5,000- $10,000 per year."

- "I am lucky to have good coverage through my employer as well as the consistency of treatment from the same pulmonologist who made the original diagnosis. He is very open to input from me regarding treatment options and regularly agrees with the course of action as I am usual willing to try anything at least once in the hopes that it might work."

- "The most expensive parts of my care are things I do not know are not covered or barely covered by insurance. Lab tests have been extremely expensive where I didn't know I'd be responsible for thousands of dollars not covered by insurance. I also was shocked at my personal expense part of a vest device so I decided not to buy/order that given uncertainties on if it would actually help clear my lungs."

Accessing Care

Across responses addressing accessing care, people shared difficulties in finding specialists and expressed frustration at the lack of bronchiectasis education in clinical practice. In addition, delayed diagnosis, travel to specialty centers, and getting care covered were shared as barriers to care.

Finding specialists / lack of bronchiectasis education

- "Education is definitely needed to other providers. I am my own advocate. I don't feel like bronchiectasis is really understood. Some healthcare providers have never heard of it."

- "It's very difficult to find experts on this condition because it is so nuanced."

Delayed Diagnosis

- "It took 2 years for me to get diagnosed properly. I wasted that time not getting the treatment I should have been having to prevent the severe lung damage I suffered"

Travel to Special Centers

- "Finding anymore in my local area has been a total nightmare. I had to travel by plane to Denver to get a diagnosis and now see a specialist about 3 1/2 hours away. All away stays for all visits are out of pocket and so is a lot of the equipment needed for daily use."

- "There are no local doctors who know anything about this. I find the best care by getting on an airplane. I have been treated at National Jewish Health and National Institutes of Health."

Trouble Getting Things Covered

- "It has been difficult to get nebulizer meds and they are expensive. I had to wait for insurance approval while I was fighting infection."

- "My main issue with getting care is getting antibiotics fast when I have a flare-up. Sometimes, my pulmonologist takes a bit of prodding, as do the pharmacies."

Hopes for a New Treatment

The following were highlighted as the most important considerations when hoping for a new treatment: improved quality of life (46%), reduced symptom burden (46%), slowing disease progression (24%), fewer side effects (10%), more convenience / lower costs (4%).

Improved Quality of Life

People highlighted both the ability to move easier and improved social life as factors that impact quality of life.

- "My hope is to be able to work full time in a career that I love, and to be able to have more energy and be as active as I want to. My hope is to be able to hike again, to be able to not live in fear of a common cold, and to know that I can plan for a long life. Above all, I hope to live a life as normally as possible, without this disease as an extra family member I have to consider before all others. I want to LIVE my life, not just survive it."

- "I would have more time and energy then to live a life that I have so longed to live . I could be more fully involved in my grandchildren's lives and that of the rest of my family. I could do more things with my friends. I would feel more comfortable, taking part in many of the activities that I currently miss out on."

Reduced Symptom Burden

The most common symptoms mentioned that people wish to reduce were exacerbations (15%), infection (11%) fatigue (4%), mucus production (8%), cough (4%), and shortness of breath (3%).

- "I would love to see a treatment with daily medication or surgery to get me back to a more normal and less sick lifestyle. I don't want to have to feel tired every day."

- "I definitely hope for a world in the near future that will provide more of a normal life for patients, including myself, where infections are not as big of a concern and life-threatening seriousness is no longer present."

- "Reduce the mucus in my lungs, so I do not develop bacterial infections (NTM). The NTM is what robs me of my time, energy and money, The bronchiectasis is the underlying condition that puts me at risk of getting NTM."

Slowing Disease Progression

- "I try to remain hopeful every day and to not let this steal my joy . I pray that someday there will be a treatment to help with symptoms and stop the progression."

- "My hopes are to experience an improvement in lung health and a more robust resilience to exacerbations, which would certainly improve my quality of life."

Fewer Side Effects

- "I would love it if there was a treatment that did not have such toxic side effects and that also had a good success rate. The current protocol has really discouraging statistics and is one reason I have been putting off starting them."

More Convenience/Lower Costs

- "Something easy to use that is not so time consuming and doesn't require special equipment."

Caregiver Impact

There was a range of support received by patients with NCFB, with 40% mentioning family, 25% mentioning no one, and 4% mentioning friends. People highlighted receiving support with transportation to appointments, help with treatments, and help with daily chores and hygiene.

- "My family is very supportive and when I am ill with a flair, I totally depend on them. This has been the most difficult piece for me as I love to be the caregiver & family helper."

- "I live alone. This will likely be a problem as I both age and my lungs basically debilitate me to the point where I can't drive or take public transit to places including the doctor or hospital."

Respondents described the impact their condition has on their caregivers and family, highlighting impacts on social life, increased family responsibilities, reduced quality of life, missed work, and time.

- “My adult son spends a great deal of time on the internet searching for the latest information about drug studies and research and anything that could possibly help. He often sits with me while I do my afternoon breathing treatments. Most people would want to be out of hearing range rather than listen to someone coughing up sputum. But we turn up the volume on the TV and watch old episodes of “Dateline” to distract us from the daily grind of lung clearance.”

- “I am very dependent on my husband who now does all the household chores and cooking for me along with holding down a full-time job. It has had such a negative impact on all our lives.”

- “Our plans for traveling are pretty much non-existent. Everyone around feels anxiety in case they might unknowingly have anything that could be contagious. A simple cold becomes a reason to cancel a visit. This disease has very much shrunk my and my husband's world.”

- “Needless to say, this condition is very stressful on my wife who is the primary caregiver. It’s only been a couple months. I can’t imagine what it will be like for her if this last several years.”

C. Clinical Guidelines

In our review, we did not find any clinical guidelines for the treatment of NCFB specific to the United States.

2019 British Thoracic Society Guideline for Bronchiectasis in Adults[7]

These guidelines pertain to adult patients with NCFB.

Imaging recommendations:

- Baseline chest x-ray in patients with suspected NCFB.
- Thin-section CT scan to confirm diagnosis of NCFB.
- Baseline imaging should occur when disease is clinically stable (as opposed to during an exacerbation).

Clinical diagnostic recommendations:

- Investigation for NCFB in patients with persistent production of mucopurulent or purulent sputum particularly with relevant associated risk factors.
- Investigation for NCFB in patients with rheumatoid arthritis if they have symptoms of chronic productive cough or recurrent chest infections.
- Investigation for NCFB in patients with COPD and a previous positive sputum culture for *P. aeruginosa* while stable then with frequent exacerbations (two or more annually).
- Investigation for NCFB in patients with inflammatory bowel disease and chronic productive cough.

Diagnostic recommendations for underlying causes of NCFB after diagnosis:

- Review for potential of rheumatoid arthritis, COPD, asthma, gastroesophageal reflux disease and inflammatory bowel disease.
- Complete blood count, serum IgE immunoglobulin, and assessment of sensitization (either serum IgE or skin prick test) to *Aspergillus fumigatus*.
- Serum Immunoglobulin G (IgG), Immunoglobulin A (IgA) and Immunoglobulin M (IgM).
- Measurement of antibody levels against *Streptococcus pneumoniae*, with immunization if deficient.
- Test for CF if there is clinical suspicion
- Test for primary ciliary dyskinesia (PCD) if there is clinical suspicion
- Sputum culture including for mycobacteria

Airway clearance:

- Breathing techniques or oscillating positive expiratory pressure.
- Gravity assisted positioning (if not contraindicated) to enhance airway clearance.

Mucoactive agents:

- Humidification with sterile water or normal saline.
- Human recombinant DNAse in the NCFB type of bronchiectasis is generally contraindicated.

Anti-inflammatory treatments:

- Routine inhaled or oral corticosteroids are generally contraindicated unless for another disorder.
- Routine phosphodiesterase type 4 (PDE4) inhibitors, methylxanthines or leukotriene receptor antagonists, CXC receptor 2 antagonists, neutrophil elastase inhibitors, and statins are generally contraindicated.

Treatments that improve outcomes in stable NCFB:

- Long-term antibiotics for patients with 3 or more exacerbations per year.
- Inhaled colistin (with inhaled gentamycin as second line and oral azithromycin/erythromycin as third line) for patients with NCFB and chronic *P. aeruginosa* infection. Oral azithromycin/erythromycin can be added to inhaled antibiotics for patients with NCFB and chronic *P. aeruginosa* infection and high exacerbation frequency.
- For patients with NCFB without chronic *P. aeruginosa* infection, azithromycin/erythromycin is first line, with inhaled gentamycin as an alternative. If macrolide allergy or resistance, doxycycline is a potential alternative.

Long-term bronchodilator use in stable NCFB:

- Any use of long-acting bronchodilator in patients with both NCFB and asthma or COPD should follow guidelines for the non-NCFB syndrome (asthma or COPD).
- Trial of long-acting bronchodilator if there is significant breathlessness.
- Reversibility testing to beta 2 agonist or anticholinergic bronchodilators may help to identify patients with co-existing asthma, although even if confirmed not to have coexisting asthma, some individuals with NCFB can still benefit from long-acting bronchodilators.

Pulmonary rehabilitation:

- Pulmonary rehabilitation should be offered to individuals functionally limited by shortness of breath.
- Inspiratory muscle training can enhance conventional pulmonary rehabilitation.

Surgery:

- Lung resection can be considered if disease is localized and symptoms are not controlled by conventional therapies.
- Multidisciplinary assessment is important in consideration of surgery to assess potential for cardiopulmonary reserve after surgery.

Lung transplantation:

- Consider transplant referral in bronchiectasis patients aged 65 years or less if the FEV_1 is <30% with significant clinical instability or if there is a rapid progressive respiratory deterioration despite optimal medical management.
- Consider earlier transplant referral in setting of massive hemoptysis, severe secondary pulmonary hypertension, ICU admissions or respiratory failure.

Immunization:

- Annual influenza and pneumococcal vaccination.

Treatment of respiratory failure:

- Long-term oxygen therapy for patients with hypoxemic respiratory failure.
- Non-invasive ventilation in the home for patients with hypercapnic respiratory failure.

Other treatments:

- Alternative treatments such as cough suppression, nutritional supplementation, complementary therapy/homeopathy, and other supplemental treatments are not routinely recommended.

Eradication of potentially pathogenic microorganisms"

- Consider eradication with clinical deterioration and new growth of *P. aeruginosa*.
- Discuss potential for eradication with clinical stability and new growth of *P. aeruginosa*.
- Consider eradication with clinical deterioration and new growth of methicillin-resistant *S. aureus* (MRSA).

Monitoring:

- All patients with NCFB should undergo routine monitoring to identify disease progression or pathogen emergence and modify treatment accordingly.

2017 European Respiratory Society Guidelines for the Management of Adult Bronchiectasis[3]

These guidelines pertain to adult patients with clinically-significant NCFB. Individuals who have radiographic bronchiectasis without clinical symptoms are not included. The guidelines make the following recommendations :

(1) For a new diagnosis of NCFB, differential blood count, serum immunoglobulins, testing for allergic bronchopulmonary aspergillosis, and sputum culture are recommended.
(2) For acute exacerbations of NCFB, 14 days of antibiotics are generally indicated, although the course can be either shortened or lengthened in specific clinical circumstances.
(3) Patients with NCFB found to have a new isolation of *P. aeruginosa* (but not other pathogens) should be offered eradication treatment.
(4) Long-term inhaled corticosteroids and statins are not routinely indicated in NCFB. Comorbid NCFB should not affect any recommendation for use of inhaled corticosteroids in patients also with asthma or COPD.
(5) For patients with NCFB and 3 or more exacerbations per year, long-term antibiotics may be indicated. For individuals with *P. aeruginosa*, the antibiotic generally should be inhaled but if an inhaled antibiotic is contraindicated, a macrolide is reasonable. Macrolides can also be added to or replace inhaled antibiotics for patients with NCFB and *P. aeruginosa* colonization who have a high exacerbation rate. For patients without *P. aeruginosa*, long-term macrolide treatment is reasonable; in this situation when macrolides are contraindicated, not tolerated, or ineffective, an alternative oral antibiotic should be based on antibiotic susceptibility and patient tolerance. If such a non-macrolide oral alternative is not tolerated in this situation, long-term inhaled antibiotic is indicated. Optimization of general aspects of NCFB management (airway clearance and treating modifiable underlying causes) should be confirmed before consideration of any long-term antibiotic therapy.
(6) Long-term mucoactive treatment is indicated for patients with NCFB who are having trouble expectorating sputum and poor quality of life and where standard airway clearance techniques have failed to control symptoms. Human recombinant DNAase is not indicated for the NCFB type of bronchiectasis.

(7) Long-term bronchodilators are not routinely indicated in NCFB, except for patients with significant breathlessness. Short-term bronchodilators are indicated before physiotherapy or before administration of inhaled mucoactive drugs and antibiotics, to improve deposition of those agents throughout the lungs. In patients with both NCFB and COPD, the use of long-acting bronchodilators should be based on an COPD-related indication only.
(8) Surgery for NCFB should only be offered if there is localized disease and high exacerbation frequency despite optimization of all other aspects of NCFB care.
(9) For patients with NCFB and chronic productive cough or difficulty expectorating sputum, airway clearance techniques should be taught by a trained therapist and performed once or twice daily. For patients with NCFB and impaired exercise capacity, pulmonary rehabilitation and regular exercise are indicated.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

The population of interest for this review was adolescents and adults with non-cystic fibrosis bronchiectasis.

We aimed to evaluate the evidence for treatment effect modification by subpopulations defined by:

- Sociodemographic factors (e.g., sex, age, race, ethnicity)
- Comorbidities (e.g., asthma, COPD)
- Pulmonary exacerbation rate in prior 12 months
- Chronic antibiotic use
- *Pseudomonas aeruginosa* culture status (positive, negative)
- Nontuberculous mycobacteria status (positive, negative)
- Bronchiectasis Severity Index Score

Interventions

The intervention of interest of this review was:

- Brensocatib (Insmed Incorporated) as add-on therapy to usual care.

Comparators

We compared brensocatib as an add-on therapy to current usual care, which may include antibiotics, mucolytics, pulmonary rehabilitation, and airway clearance, versus usual care alone.

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Pulmonary exacerbations
    - Exacerbation-related hospitalization or emergency room visit
    - Quality of life (e.g., quality of life-bronchiectasis questionnaire)
    - Lung function (e.g., FEV_1)
    - Use of rescue medications, such as bronchodilators
    - All-cause mortality
- Other Outcomes
    - Changes in biomarkers (e.g., neutrophil elastase)
- Adverse events (AEs) including but not limited to:
    - Serious AEs
    - Discontinuation due to AEs
    - Other AEs of interest
        - Hyperkeratosis
        - Severe infection
        - Pneumonia
        - Gum disease

Timing

Evidence on intervention effectiveness and harms was derived from studies of any duration.

Settings

All relevant settings were considered, with a focus on outpatient settings in the United States.

Study Design

Randomized controlled trials and non-randomized controlled trials with any sample size were included. High-quality comparative observational studies were also included.

Table D1.1 PRISMA 2020 Checklist

Section and Topic	Item #	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information Sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search Strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect Measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.

Section and Topic	Item #	Checklist Item
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study Characteristics	17	Cite each included study and present its characteristics.
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
OTHER INFORMATION		

Section and Topic	Item #	Checklist Item
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing Interests	26	Declare any competing interests of review authors.
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for non-cystic fibrosis bronchiectasis followed established best research methods.[80,81] We reported the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[82] The PRISMA guidelines include a checklist of 27 items (see Table D1.1).

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews.

Table D1.2. Ovid MEDLINE(R) ALL, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews Search Strategy

#	Search Terms
1	exp bronchiectasis/
2	("bronchiectases" OR "bronchiectasia" OR "bronchiectasis" OR "bronchiectasis, cylindrical" OR "bronchiectasis, cystic" OR "bronchiectasis, saccular" OR "bronchiectasis, varicose" OR "bronchoectasia" OR "congenital bronchiectasis" OR "cylindrical bronchiectases" OR "cylindrical bronchiectasis" OR "cystic bronchiectasis" OR "NCFB" OR "non-CF bronchiectasis" OR "noncystic fibrosis bronchiectasis" OR "non-cystic fibrosis bronchiectasis" OR "saccular bronchiectases" OR "saccular bronchiectasis" OR "varicose bronchiectases" OR "varicose bronchiectasis").ti,ab.
3	1 OR 2
4	("brensocatib" OR "azd 7986" OR "azd7986" OR "azd-7986" OR "ins 1007" OR "ins1007" OR "ins-1007").ti,ab.
5	3 and 4
6	5 NOT (animals not (humans and animals)).sh.
7	6 NOT (addresses OR autobiography OR bibliography OR biography OR comment OR congresses OR consensus development conference OR dictionary OR directory OR duplicate publication OR editorial OR encyclopedia OR festschrift OR guideline OR interactive tutorial).pt
8	limit 7 to English language
9	Remove duplicates from 8

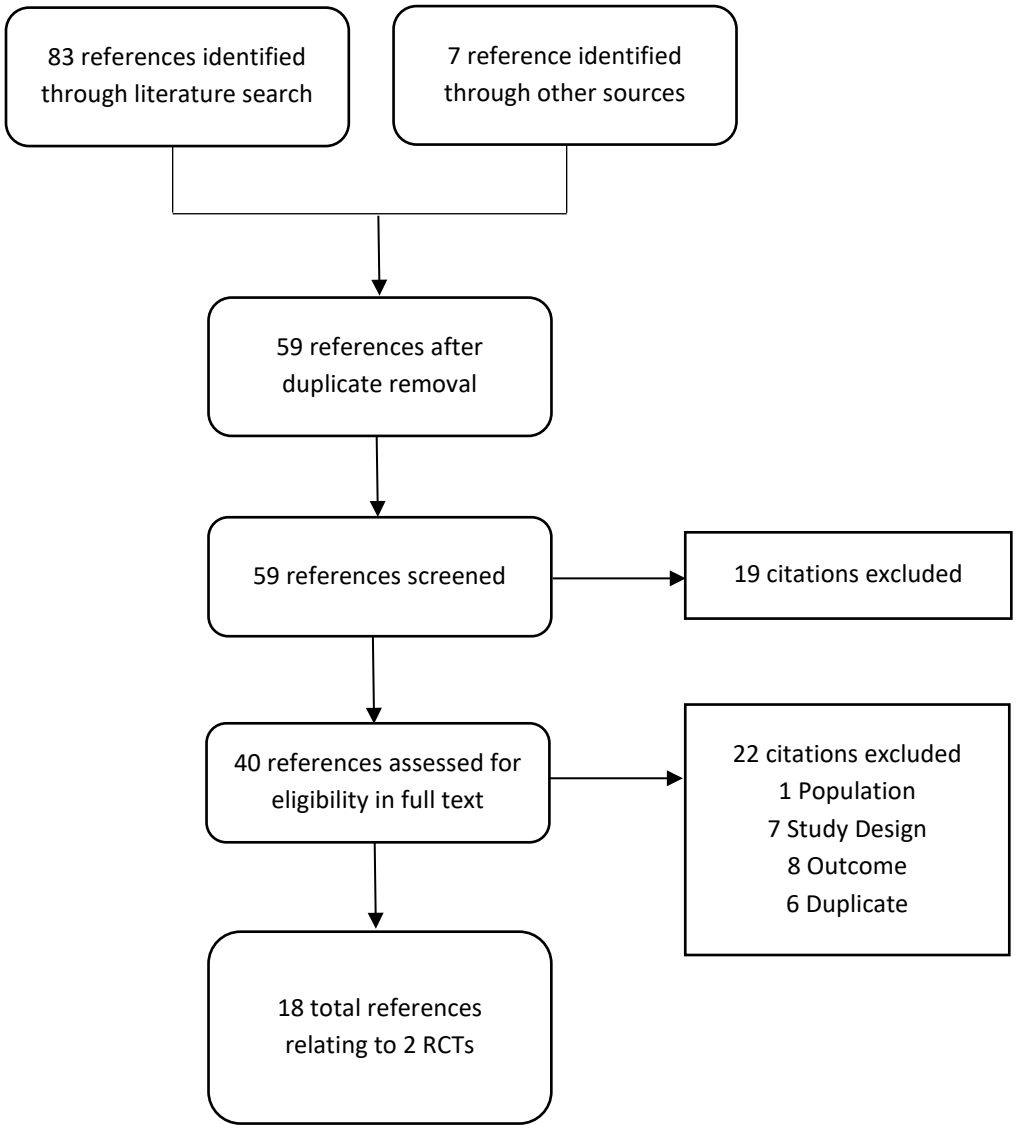
Date of last search: April 16, 2025

Table D2.2. EMBASE Search Strategy

#	Search Terms
1	'bronchiectasis'/exp
2	('bronchiectases' OR 'bronchiectasia' OR 'bronchiectasis' OR 'bronchiectasis, cylindrical' OR 'bronchiectasis, cystic' OR 'bronchiectasis, saccular' OR 'bronchiectasis, varicose' OR 'bronchoectasia' OR 'congenital bronchiectasis' OR 'cylindrical bronchiectases' OR 'cylindrical bronchiectasis' OR 'cystic bronchiectasis' OR 'NCFB' OR 'non-CF bronchiectasis' OR 'noncystic fibrosis bronchiectasis' OR 'non-cystic fibrosis bronchiectasis' OR 'saccular bronchiectases' OR 'saccular bronchiectasis' OR 'varicose bronchiectases' OR 'varicose bronchiectasis'):ti,ab
3	#1 OR #2
4	('brensocatib' OR 'azd 7986' OR 'azd7986' OR 'azd-7986' OR 'ins 1007' OR 'ins1007' OR 'ins-1007'):ti,ab
5	#3 and #4
6	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
7	#5 NOT #6
8	#7 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
9	#8 AND [english]/lim

Date of last search: April 16, 2025

Figure D1.1. PRISMA Flow Chart Showing Results of Literature Search for Brensocatib



Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge (Nested Knowledge, Inc, St. Paul, MN); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. Two investigators reviewed full papers and provided justification for exclusion of each excluded study.

We also included data submitted by the manufacturer. All literature that did not undergo a formal peer review process is described separately.

Data Extraction

Data were extracted into Microsoft Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

Risk of Bias Assessment

We examined the risk of bias for each randomized trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[81,83] Risk of bias was assessed by study outcome for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers independently assessed these domains. Any disagreements were resolved through discussion or by consulting a third reviewer. We did not assess the risk of bias in trials where we only had access to conference abstracts/presentations.

To assess the risk of bias in trials, we rated the categories as: “low risk of bias,” “some concerns,” or “high risk of bias.” Guidance for risk of bias ratings using these criteria is presented below:

***Low risk of bias**: The study is judged to be at low risk of bias for all domains for this result.*

***Some concerns**: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.*

***High risk of bias**: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.*

We examined the risk of bias for the following outcomes: the annualized rate of pulmonary exacerbations, time to first exacerbation, and QoL-B Respiratory Symptom Score. See Table D1.3.

Table D1.3. Risk of Bias Assessment

Outcomes	Randomization Process	Deviation from Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
ASPEN Trial						
Annualized Rate of Exacerbations	Low	Low	Low	Low	Low	Low
Time to First Exacerbation	Low	Low	Low	Low	Low	Low
QoL-B Respiratory Symptom Score	Low	Low	Low	Low	Low	Low
WILLOW Trial						
Annualized Rate of Exacerbations	Low	Low	Low	Low	Low	Low
Time to First Exacerbation	Low	Low	Low	Low	Low	Low
QoL-B Respiratory Symptom Score	Low	Low	Low	Low	Low	Low

QoL-B: Quality of Life Questionnaire – Bronchiectasis

Evaluation of Subgroup Credibility

We planned to evaluate the credibility of clinically relevant subgroup analyses (aka effect modification analyses) using criteria published in the Instrument for the Credibility of Effect Modification ANalyses (ICEMAN) tool (Version 1.1).[84]

Based on patient and clinical expert input, we highlighted the following subgroups in our protocol:

- Sociodemographic factors (e.g., sex, age, race, ethnicity)
- Comorbidities (e.g., asthma, COPD)
- Pulmonary exacerbation rate in prior 12 months
- Chronic antibiotic use
- *Pseudomonas aeruginosa* culture status (positive, negative)
- Nontuberculous mycobacteria status (positive, negative)
- Bronchiectasis Severity Index Score

Based on feedback from patient organizations, we added use of chronic macrolides and eosinophil phenotype/endotype.

Data on these subgroups aside from NTM status were available for the outcome of annualized rate of exacerbations. These subgroups were explored for other outcomes in non-peer reviewed conference posters and presentations.[22,24-26,85]

The Phase III ASPEN trial was not powered to detect treatment differences in the prespecified subgroups. In addition, there were no interaction p-values reported. The trial concludes the results of the subgroup analyses for annualized exacerbation rates were generally consistent with overall estimate for both doses of brensocatib. Therefore, we did not formally evaluate the credibility of these subgroup analyses using the ICEMAN tool.

Evaluation of Clinical Trial Diversity

We evaluated the demographic diversity of clinical trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[29] The CDR tool was designed to evaluate the three demographic characteristics described in Table D1.5. Representation for each demographic category was evaluated by quantitatively comparing clinical trial participants with disease-specific prevalence estimates,[86] using the metric "Participant to Disease-prevalence Representation Ratio" (PDRR). Next, a representation score between 0 to 3 was assigned based on the PDRR estimate (See Table D1.6 for the PDRR cut points that correspond to each representation score). Finally, based on the total score of the demographic characteristics (e.g., race and ethnicity), the categories "Good," "Fair," or "Poor" are used to communicate the overall level of diversity of a clinical trial. The description of the rating categories for each demographic characteristic is provided in Table D1.7.

Table D1.4. Demographic Characteristics and Categories

Demographic Characteristics	Categories
1. Race and Ethnicity*	Racial categories: • White • Black or African American • Asian • American Indian and Alaskan Native • Native Hawaiian and Other Pacific Islanders Ethnic Category: • Hispanic or Latino
2. Sex	• Female • Male
3. Age	• Older adults (≥65 years)

*Multinational trials: For multinational clinical trials, our approach is to evaluate only the subpopulation of patients enrolled from the US on racial and ethnic diversity

Table D1.5. Representation Score

Participant to Disease-Prevalence Representation Ratio (PDRR)	Score
0	0
>0 and Less Than 0.5	1
0.5 to 0.8	2
≥0.8	3

Table D1.6. Rating Categories

Demographic Characteristics	Demographic Categories	Maximum Score	Rating Categories (Total Score)
Race and Ethnicity*	Asian, Black or African American, White, and Hispanic or Latino	12	Good (11-12) Fair (7-10) Poor (≤6)
Sex	Male and Female	6	Good (6) Fair (5) Poor (≤4)
Age	Older adults (≥65 years)	3	Good (3) Fair (2) Poor (≤1)

*American Indian or Alaskan Native & Native Hawaiian or Other Pacific Islander are not factored into the overall racial and diversity rating. However, information on enrollment and PDRR estimates are reported when reliable prevalence estimates are available.

Results

Table D1.7. Diversity Ratings on Race and Ethnicity, Sex, and Age (Older Adults)

Trial	Race and Ethnicity	Sex	Age (Older adults)
ASPEN	Fair	Good	NE
WILLOW	Fair	Good	NE

NE: Not Estimated

Table D1.8. presents the clinical trial diversity ratings on race and ethnicity, sex, and age (older adults) for 2 trials.

We requested data from the manufacturers on demographic data specific to the United States portion of the study as it was a multinational trial, but we did not receive this data. Therefore, we used the overall trial data on race and ethnicity, sex, and age to compare to the US prevalence of NCFB for each subgroup.

Race and Ethnicity: Ratings are based on multinational clinical trial data and the prevalence of NCFB by race or ethnicity in the United States. Both trials had "Fair" representation of race and ethnicity as they adequately represented white and Asian individuals with bronchiectasis, but the ASPEN trial underrepresented Black individuals with bronchiectasis and the WILLOW trial underrepresented both Black and Hispanic individuals with bronchiectasis.[8,19,86] See Table D1.9.

Sex: Ratings are based on multinational clinical trial data and the prevalence of NCFB in male and female sex the United States. Both trials adequately represented male and female sex and thus both studies were rated as "Good".[8,19,86] See Table D1.9.

Age: Reliable prevalence estimates for adults 65 years of age or older in the United States were not available, thus no rating could be generated. However, it is known that the prevalence of NCFB increases with age and at least half of the participants enrolled in both trials were 65 years of age or older.[8,19]

Table D1.8. Total Score and Diversity Rating by Race/Ethnicity, Sex, and Age

	Race/Ethnicity						Sex				Age		
	White	Black/ African American	Asian	Hispanic/ Latino	Total Score	Diversity Rating	Male	Female	Total Score	Diversity Rating	≥65 Years	Total Score	Diversity Rating
US Prevalence[86]	89.5%	2.5%	3.7%	4.3%			21.0%	79.0%			NR		
ASPEN Trial Prevalence	73.6%	0.6%	11.1%	29.7%	10	Fair	35.7%	64.3%	6	Good	48.8%	NE	NE
PDRR	0.82	0.23	3.00	6.91			1.70	0.81			NE		
Score	3	1	3	3			3	3			NE		
WILLOW Trial Prevalence	87.9%	1.6%	9.0%	2.3%	10	Fair	32.0%	68.0%	6	Good	58.6%	NE	NE
PDRR	0.98	0.63	2.43	0.55			1.53	0.86			NE		
Score	3	2	3	2			3	3			NE		

NR: Not Reported, NC: Not Calculated, NE: Not Estimated, PDRR: Participant to Disease-prevalence Representation Ratio

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[87,88]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for these newer treatments, we scanned the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include: "non-cystic fibrosis bronchiectasis," "brensocatib," and "INS1007". We selected studies which would have met our inclusion criteria, and for which no findings have been published. We provided a qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

Data Synthesis and Statistical Analyses

Relevant data on key outcomes of the main studies were summarized qualitatively in the body of the Evidence Report and in evidence tables (Supplement Section D3).

D2. Additional Clinical Evidence

Additional Methods

WILLOW

WILLOW was a 24-week Phase II multi-national, randomized trial that evaluated two doses of brensocatib (10 mg and 25 mg) compared to placebo. Participants were randomized 1:1:1 to either dose of brensocatib or placebo. Participants were eligible if they were between 18 and 85 years of age with a clinical history consistent with NCFB (e.g., cough, chronic production of sputum, and respiratory infection) as confirmed by chest computed tomography (CT) scan. Participants were required to be able to produce sputum with a history of chronic expectoration and a history of at least two pulmonary exacerbations in the 12 months prior to screening. Participants were excluded if they had a primary diagnosis of either COPD or asthma, bronchiectasis due to cystic fibrosis, were current smokers, were being treated for nontuberculous mycobacterial lung infection, allergic bronchopulmonary aspergillosis, or tuberculosis, or had any acute infections.[19,89]

The primary outcome of the WILLOW trial was the time of the first pulmonary exacerbation up to 24 weeks. Key secondary outcomes included: the rate of exacerbations, change from baseline in post-bronchodilator FEV_1, Quality of Life-Bronchiectasis (QoL-B) Respiratory Symptom score, and the concentration of neutrophil elastase in sputum at 24 weeks.[19]

Enrolled participants were around 64 years of age with over half exceeding the age of 65, predominantly white, and 68% female. The median bronchiectasis severity index (BSI) score was 8 indicating moderate bronchiectasis with 33% of participants experiencing 3 or more exacerbations in the past 12 months and 36% being hospitalized in the past 24 months. A third were positive for *Pseudomonas aeruginosa*.[19]

Additional Results

ASPEN

Annualized Rate of Exacerbations

A tipping-point and jump-to-reference analysis were conducted on the primary outcome to explore the strength of the primary analysis results. Results from each analysis were similar to primary analysis results and did not shift the conclusions.[8]

Post-Bronchodilator Forced Vital Capacity (FVC)

The change from baseline in post-bronchodilator FVC at week 52 was a prespecified exploratory outcome. The least square mean post-bronchodilator FVC was -51, -12, and -87 for brensocatib 10 mg, brensocatib 25 mg, and placebo, respectively (10 mg difference vs placebo: 36 [95%CI: 3, 69]; 20 mg difference vs placebo: 75 [95%CI: 40, 110]).[8]

WILLOW

Primary Outcome

Time to First Exacerbation

Due to low numbers of exacerbations in the brensocatib arms, the median time to first exacerbation was not estimated. The median time to first exacerbation in the placebo group was 189 days. Participants who received either dose of brensocatib had a longer time to first exacerbation compared to placebo (10 mg versus placebo HR: 0.58; p=0.03; 25 mg versus placebo HR: 0.62; p=0.04).[19]

Bronchiectasis Exacerbation and Symptoms Tool (BEST) Score

The BEST questionnaire is a patient-reported diary that was completed by adult participants daily with the goal of tracking day-to-day symptom changes and detecting exacerbations. Scores range from 0 to 26 which lower scores indicating less symptoms.[27,34]

Data on BEST scores at baseline were not available. Participants in the brensocatib groups had numerically greater changes in the BEST score from baseline to week 52 compared to placebo but these results did not meet the proposed MCID of a 4-point decrease versus placebo. [8,34]

Secondary Outcomes

Rate of Exacerbations

During the 24-week trial, there were 34, 42, and 54 exacerbations in the 10 mg, 25 mg, and placebo groups, respectively. The exacerbations per person-year were 0.88 for the 10 mg group, 1.03 for 25mg, and 1.37 for placebo. While there were numerically less exacerbations for participants who received brensocatib than placebo, the rate versus placebo was statistically significant for the 10 mg group (RR: 0.64; 95%CI: 0.42 – 0.98; p=0.04) but not 25 mg (RR: 0.75; 95%CI: 0.5 – 1.13; p=0.17).[19]

A higher percentage of participants who received brensocatib remained exacerbation-free during the trial (10 mg: 68%, 25 mg 67%) compared to placebo (52%) [10 mg versus placebo p-value: 0.03, 25 mg versus placebo p-value: 0.04].[19]

Severe Exacerbations

There were less severe exacerbations reported in the 10 mg brensocatib (5) and 25 mg brensocatib (4) groups than the placebo group (10), with an unadjusted annualized rates of 0.19, 0.11, and 0.30, respectively.[19]

Sputum Biomarkers

The mean sputum neutrophil elastase levels were lower among both brensocatib groups than with placebo during the 24-week trial. At week 28 after the treatment period ended, the mean change in sputum neutrophil elastase for all three groups returned back to baseline values.[19]

Additional sputum biomarkers were evaluated in secondary publications and results concluded the potential for broad anti-inflammatory effects beyond neutrophil elastase.[90-92]

Post Bronchodilator FEV_1

The two brensocatib groups had a -0.3 percentage point change in post-bronchodilator FEV_1 and the placebo group had a -1.8 percentage point change, leading to a mean difference of 1.5 percentage points in each brensocatib group versus placebo.[19]

Quality of Life-Bronchiectasis Respiratory Symptom Score (QoL-B RSS)

The least squares mean change from baseline for the QoL-B RSS domain was 3.8, 5.9, and 5.7 for brensocatib 10 mg, brensocatib 25 mg, and placebo, respectively. These changes did not reach the MCID of eight points versus placebo.[19] Data on other domains of the QoL-B assessment are reported in Supplement Table D3.5.

Additional Harms

WILLOW

During the 24-week trial, adverse events experienced by participants were mostly mild to moderate with 93% experiencing at least one in the 10 mg brensocatib arm, 83% in the 25 mg brensocatib arm, and 79% in the placebo arm. When excluding bronchiectasis exacerbations, rates of adverse events were higher in the brensocatib groups compared to placebo (10 mg: 63%, 25 mg: 54%, placebo: 38%). Rates of serious adverse events were higher in the placebo arm. The most common adverse events were cough, headache, increased sputum, and shortness of breath. Headache and shortness of breath occurred more frequently in the 25 mg brensocatib arm. Adverse events of special interest due to the mechanism of action of brensocatib were skin events, which occurred more frequently in the 25 mg brensocatib arms compared to placebo, and dental events, which occurred more frequently in the 10 mg brensocatib arm compared to placebo. Adverse events

leading to study drug or trial discontinuation were similar across arms. One death occurred in the 25 mg brensocatib group.[19]

D3. Evidence Tables

Table D3.1. Study Design

Study Design	Inclusion/Exclusion Criteria	Outcomes
ASPEN Trial (NCT04594369)		
Design: Phase 3 randomized, double-blind, placebo-controlled, parallel-group, multicenter, multi-national, 52-week trial **Enrolled N: 1,767** **Treatment Arms*:** **1. Brensocatib 10 mg** **2. Brensocatib 25 mg** **3. Placebo** ***All administered as a once daily oral tablet*** **Locations (35): United States, Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Denmark, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, Korea, Latvia, Malaysia, Mexico, Netherlands, New Zealand, Peru, Poland, Portugal, Serbia, Slovakia, Spain, Taiwan, Thailand, Turkey,**	Inclusion Criteria: • Age: 12 to 85 years • Clinical history consistent with non-cystic fibrosis bronchiectasis (NCFBE) (cough, chronic sputum production and/or recurrent respiratory infections) confirmed by chest computerized tomography scan within 5 years before screening • ≥2 pulmonary exacerbations (PE) defined by need for antibiotic prescription by a physician for the signs and symptoms of respiratory infections in the past 12 months before Screening • Adolescent participants are required to have ≥1 PE in the prior 12 months • Use of contraception also detailed Exclusion Criteria: • A primary diagnosis of COPD or asthma as judged by the Investigator • Bronchiectasis due to cystic fibrosis. • Current smokers as defined per Centers for Disease Control • Known or suspected immunodeficiency disorder, including history of invasive opportunistic infections. • Known history of human immunodeficiency virus infection. • Currently being treated for nontuberculous mycobacterial lung infection, allergic bronchopulmonary aspergillosis, or tuberculosis. • Active and current symptomatic infection by COVID-19 • Receiving medications/therapy prohibited as concomitant medications • Previously participated in a clinical trial for brensocatib. • Received any live attenuated vaccine within 4 weeks prior to the first administration of brensocatib • Suffering an exacerbation 4 weeks before Screening or during Screening	Primary Outcome: • Rate of Adjudicated Pulmonary Exacerbations (PEs) [52 weeks] Secondary Outcomes: • Time to First Adjudicated PE [52 Weeks] • Percentage of PE-Free Participants [52 Weeks] • Change From Baseline in Postbronchodilator FEV_1 [Baseline, at Week 52] • Rate of Severe Adjudicated PEs [52 Weeks] • Change from Baseline to Week 52 in Quality of Life Questionnaire - Bronchiectasis (QOL-B) Respiratory Symptoms Domain Score in Adult Participants [Baseline to Week 52] • Number of Participants who Experience ≥1 TEAE [56 Weeks] • Plasma Concentration of Brensocatib at Select Time Points [Pre-dose and post-dose at multiple time points up to Week 52]

Study Design	Inclusion/Exclusion Criteria	Outcomes
Ukraine†, United Kingdom	• Participated in any other interventional clinical studies within 3 months before Screening • History of alcohol or drug abuse within 6 months prior to Screening. • Known history of hypersensitivity to brensocatib or any of its excipients. • *Subjects receiving supplemental oxygen > 12 hours per day* • Started oral or inhaled antibiotics as chronic treatment for NCFBE <3 months prior to the Screening Visit.	
WILLOW Trial (NCT03218917)		
Design: Phase 2 randomized, double-blind, placebo-controlled, parallel-group, multicenter, multi-national, 24-week trial **Enrolled N: 256** **Treatment Arms:** **1. Brensocatib 10 mg** **2. Brensocatib 25 mg** **3. Placebo** ***All administered as a once daily oral tablet*** **Locations: United States, Australia, Bulgaria, Denmark, Germany, Italy, Korea, Netherlands, New Zealand, Poland, Singapore, Spain, United Kingdom**	Inclusion Criteria: • Age: 18 to 85 years • Clinical history consistent with NCFBE (cough, chronic sputum production and/or recurrent respiratory infections) confirmed by chest computed tomography • Current sputum producers with a history of chronic expectoration and able to provide a sputum sample during Screening • Have ≥2 documented pulmonary exacerbations in the past 12 months before Screening Exclusion Criteria: • Have a primary diagnosis of COPD or asthma • Have bronchiectasis due to cystic fibrosis, hypogammaglobulinemia, common variable immunodeficiency, or alpha1-antitrypsin deficiency • Current smokers • Currently being treated for a nontuberculous mycobacterial lung infection, allergic bronchopulmonary aspergillosis, or tuberculosis • Have any acute infections, (including respiratory infections)	Primary Outcome: • Time to the First Pulmonary Exacerbation [Baseline to Week 24] Secondary Outcomes: • Number of Participants Who Experienced a Pulmonary Exacerbation [Baseline to Week 24] • Change From Baseline in Quality of Life Questionnaire - Bronchiectasis (QOL-B) Respiratory Symptoms Domain Score [Baseline to Week 24] • Change From Screening in Post-Bronchodilator Percent Predicted FEV_1 [Screening (Days -42 to -1) to Week 24] • Change From Baseline in Concentration of Active Neutrophil Elastase (NE) in Sputum [Baseline to Week 24]

COPD: chronic obstructive pulmonary disease, FEV_1: forced expiratory volume in one second, mg: milligram, N: total number, NCFBE: non-cystic fibrosis bronchiectasis, NE: neutrophil elastase, PE: pulmonary exacerbation, QOL-B: Quality of Life Questionnaire - Bronchiectasis

*Adults randomized 1:1:1 to the three arms, adolescents randomized 2:2:1
†Data from 44 patients not included due to ongoing military conflict in Ukraine.

Table D3.2. Baseline Characteristics

Trial		ASPEN[8]			WILLOW[19,23]		
Arm		**Brensocatib 10 mg**	**Brensocatib 25 mg**	**Placebo**	**Brensocatib 10 mg**	**Brensocatib 25 mg**	**Placebo**
N		**583**	**575**	**563**	**82**	**87**	**87**
Demographic Characteristics							
Age, Years	Mean (SD)	59.8 (15.9)	60.6 (15.8)	60.0 (15.4)	64.6 (12.4)	63.7 (12.7)	64.0 (11.9)
	> 65	277 (47.5)	302 (52.5)	260 (46.2)	48 (58.5)	48 (55.2)	54 (62.1)
	≥75	83 (14.2)	84 (14.6)	93 (16.5)	20 (24.4)	14 (16.1)	14 (16.1)
	18 to 74	483 (82.8)	475 (82.6)	462 (82.1)	NR	NR	NR
	< 18	17 (2.9)	16 (2.8)	8 (1.4)	NR	NR	NR
Sex	Female	385 (66.0)	360 (62.6)	362 (64.3)	57 (70)	62 (71)	55 (63)
	Male	198 (34.0)	215 (37.4)	201 (35.7)	25 (30)	25 (29)	32 (37)
Race/Ethnicity	American Indian/ Alaska Native	8 (1.4)	6 (1.0)	9 (1.6)	0	0	0
	Asian	63 (10.8)	64 (11.1)	64 (11.4)	5 (6.1)	5 (5.7)	13 (14.9)
	Black/African American	2 (0.3)	5 (0.9)	3 (0.5)	0.0	2 (2.3)	2 (2.3)
	Hispanic/Latino	177 (30.4)	164 (28.5)	170 (30.2)	2 (2.4)	4 (4.6)	0
	Native Hawaiian/ Pacific Islander	1 (0.2)	0	1 (0.2)	1 (1.2)	1 (1.1)	1 (1.1)
	White	431 (73.9)	430 (74.8)	405 (71.9)	76 (93)	78 (90)	71 (82)
	Unknown/NR/Other	53 (9.1)	50 (8.7)	60 (10.7)	0	Other: 1 (1.1)	0
	More than one race or ethnic group	25 (4.3)	20 (3.5)	21 (3.7)	NR	NR	NR
BMI (kg/m^2)	Mean (SD)	25.5 (5.4)	25.4 (5.1)	25.1 (4.9)	NR	NR	NR
Disease Characteristics							
Bronchiectasis Severity Index (BSI)	Mean (SD)	7.1 (3.5)	7.1 (3.6)	7.1 (3.6)	NR	NR	NR
	Medium (range)	NR	NR	NR	8 (1, 21)	8 (0, 19)	7 (0, 19)
	≤ 4	136 (23.3)	150 (26.1)	148 (26.3)	NR	NR	NR
	5 to 8	275 (47.2)	239 (41.6)	220 (39.1)	NR	NR	NR
	≥ 9	168 (28.8)	182 (31.7)	195 (34.6)	NR	NR	NR

Trial		ASPEN[8]			WILLOW[19,23]		
Arm		Brensocatib 10 mg	Brensocatib 25 mg	Placebo	Brensocatib 10 mg	Brensocatib 25 mg	Placebo
N		583	575	563	82	87	87
Exacerbations in Prior 12 Months	Mean (SD)	NR	NR	NR	NR	NR	NR
	2	411 (70.5)*	412 (71.7)*	396 (70.3)*	NR	NR	NR
	≥3	172 (29.5)	163 (28.3)	167 (29.7)	23 (28)	36 (41)	25 (29)
Hospitalization in Prior 24 Months	Exacerbation-related	146 (25.0)	133 (23.1)	142 (25.2)	31 (38)	31 (36)	30 (34)
Comorbidities	Asthma	101 (17.3)	109 (19.0)	111 (19.7)	18 (22)	21 (24)	25 (29)
	COPD	77 (13.2)	83 (14.4)	102 (18.1)	12 (15)	13 (15)	17 (20)
Smoking History	Yes	164 (28.1)	163 (28.3)	183 (32.5)	NR	NR	NR
Pseudomonas Aeruginosa Culture Status	Positive	203 (34.8)	205 (35.7)	199 (35.3)	27 (33)	33 (38)	29 (33)
Blood Eosinophil Count	<300 cells/mcL	465 (79.8)	461 (80.2)	452 (80.3)	NR	NR	NR
	≥300 cells/mcL	115 (19.7)	111 (19.3)	106 (18.8)	NR	NR	NR
Post-BDR FEV_1 % Predicted	Mean (SD)	74.3 (23.4)†	74.3 (24.6)†	71.9 (22.2)	65.9 (23.9)	70.0 (23.2)	67.3 (23.9)
MRC Dyspnea Score	1 to 3	NR	NR	NR	NR	NR	NR
	4	NR	NR	NR	NR	NR	NR
	5	NR	NR	NR	NR	NR	NR
QOL-B RSS	Mean (SD)	59.8 (17.0)‡	61.9 (17.2)‡	60.0 (16.8)‡	NR	NR	NR
Bronchiectasis Etiology	Idiopathic or other	331 (56.8)	354 (61.6)	321 (57.0)	NR	NR	NR
	Post-infective (pneumonia/childhood infection)	173 (29.7)	156 (27.1)	174 (30.9)	NR	NR	NR
	Primary ciliary dyskinesia	47 (8.1)	38 (6.6)	33 (5.9)	NR	NR	NR
Baseline Treatment Use	Long-term antibiotics	146 (25.0)	154 (26.8)	133 (23.6)	NR	NR	NR
	Long-term macrolides	110 (18.9)	114 (19.8)	105 (18.7)	10 (12)	16 (18)	14 (16)
	Long-term inhaled antibiotics	41 (7.0)	40 (7.0)	36 (6.4)	NR	NR	NR

Trial		ASPEN[8]			WILLOW[19,23]		
Arm		Brensocatib 10 mg	Brensocatib 25 mg	Placebo	Brensocatib 10 mg	Brensocatib 25 mg	Placebo
N		583	575	563	82	87	87
	Inhaled glucocorticoids	324 (55.6)	324 (56.3)	352 (62.5)	43 (52)	49 (56)	52 (60)

Units are n (%) unless otherwise specified. BDR: bronchodilator, BSI: bronchiectasis severity score, COPD: chronic obstructive pulmonary disease, FEV_1: forced expiratory volume in one second, mg: milligram, n: number, N: total number, NR: not reported, SD: standard deviation

*Adolescents with one exacerbation (8 adolescents in the 10-mg brensocatib group, 9 in the 25-mg brensocatib group, and 4 in the placebo group) were included in the two-exacerbations category.

†Baseline FEV_1 values were not available for 4 participants in the 10-mg brensocatib group and 4 in the 25-mg brensocatib group.

‡QOL-B RSS questionnaire was administered to adult patients only, and scores were not available for 78 of 566 adults in the 10-mg brensocatib group, 62 of 559 adults in the 25-mg brensocatib group, and 68 of 555 adults in the placebo group.

Table D3.3. Study Disposition

Trial	ASPEN[8]			WILLOW[19]		
Arm	**Brensocatib 10 mg**	**Brensocatib 25 mg**	**Placebo**	**Brensocatib 10 mg**	**Brensocatib 25 mg**	**Placebo**
ITT Analysis	583	575	563	82	87	87
Safety Analysis	582*	574*	563	81	89†	85‡
Completed Study	458 (78.6)	466 (81.0)	457 (81.2)	76 (92.7)	75 (86.2)	74 (85.1)
Ongoing Study	47 (8.1)	44 (7.7)	31 (5.5)	NR	NR	NR
Ongoing Treatment	9 (1.5)	7 (1.2)	4 (0.7)	NR	NR	NR
Study Discontinuation by Reason						
Overall	78 (13.4)	65 (11.3)	75 (13.3)	6 (6.9)	12 (13.8)	13 (14.9)
Adverse Events	10 (1.7)	10 (1.7)	9 (1.6)	3 (3.4)	3 (3.4)	2 (2.3)
Death	2 (<1)	4 (<1)	8 (1.4)	0	1 (1.1)	0
Lost to Follow-Up	10 (1.7)	2 (<1)	4 (<1)	1 (1.1)	0	0
Physician Decision	2 (<1)	2 (<1)	3 (<1)	0	1 (1.1)	1 (1.1)
Protocol Deviation	1 (<1)	3 (<1)	2 (<1)	0	0	0
Patient Withdrawal	40 (6.9)	32 (5.6)	37 (6.6)	2 (2.3)	4 (4.6)	10 (11.5)
Study Drug Noncompliance	NR	NR	NR	0	1 (1.1)	0
Other	13 (2.2)	12 (2.1)	12 (2.1)	0	2 (2.3)	0

Units are n (%) unless otherwise specified. mg: milligram, n: number, N: total number, NR: not reported

*Two patients (one in each brensocatib arm) did not receive the drug and were not included in the safety analysis set.

†One patient in the placebo and 10 mg brensocatib arms incorrectly received 25 mg brensocatib. Both were included as originally randomized for the intention-to-treat population and included as part of the 25 mg brensocatib arm for the safety analysis. Both patients were discontinued once the error was identified. Patients were included as originally randomized in the intention-to-treat population, and in the safety population they were included in the 25 mg brensocatib group as per the drug received.

‡One patient randomized to placebo never received study drug

Table D3.4. Efficacy: Exacerbation-Related Outcomes

Trial		ASPEN[8,23]			WILLOW[19,23,89]		
Arm		**Brensocatib 10 mg**	**Brensocatib 25 mg**	**Placebo**	**Brensocatib 10 mg**	**Brensocatib 25 mg**	**Placebo**
N		**583**	**575**	**563**	**82**	**87**	**87**
Timepoint		**52 Weeks**			**24 Weeks**		
Exacerbation-Related Outcomes							
Any Exacerbations	No. exacerbations	NR	NR	NR	34	42	54
	n (%) with ≥1 exacerbation	NR	NR	NR	26 (32)	29 (33)	42 (48)
	Annualized Rate (95%CI)	1.02 (0.91, 1.13)	1.04 (0.93, 1.16)	1.29 (1.16, 1.43)	0.88 (0.61, 1.26)	1.03 (0.75, 1.42)	1.37 (1.02, 1.84)
	Rate Ratio (95%CI); p-value vs. placebo	0.79 (0.68, 0.92); p=0.004	0.81 (0.69, 0.94); p=0.005	reference	0.64 (0.42, 0.98); p=0.04	0.75 (0.50, 1.13); p=0.17	reference
Severe Exacerbations	No. exacerbations	NR	NR	NR	5	4	10
	n (%) with ≥1 exacerbation	NR	NR	NR	NR	NR	NR
	Annualized Rate (95%CI)	0.14 (0.10, 0.18)	0.14 (0.11, 0.18)	0.19 (0.14, 0.24)	0.19[†]	0.11[†]	0.3[†]
	Rate Ratio (95%CI); p-value vs. placebo	0.74 (0.51, 1.09); NA*	0.74 (0.52, 1.06); p=0.21	reference	NR	NR	NR
Time to First Exacerbation, Weeks	N at risk	183	169	154	53	52	38
	Median (95%CI)	49.0 (NR)[§]	50.7 (NR)[§]	36.7 (NR)[§]	NE[‡]	NE[‡]	27 (NR)
	Hazard Ratio (95%CI); p-value vs. placebo	0.81 (0.70, 0.95); p=0.02	0.83 (0.70, 0.97); p=0.04	reference	0.58 (NR); p=0.03	0.62 (NR); p=0.04	reference
Exacerbation-Free	n (%) with no exacerbations	283 (48.5)	279 (48.5)	227 (40.3)	56 (68)	58 (67)	45 (52)
	Rate Ratio (95%CI); p-value vs. placebo	1.20 (1.06, 1.37); p=0.02[#]	1.18 (1.04, 1.34); p=0.04[#]	reference	NR	NR	NR
Sensitivity Analysis: Reference Based Multiple Imputation (Intention-to-Treat)							

Trial		ASPEN[8,23]			WILLOW[19,23,89]		
Arm		Brensocatib 10 mg	Brensocatib 25 mg	Placebo	Brensocatib 10 mg	Brensocatib 25 mg	Placebo
N		583	575	563	82	87	87
Timepoint		52 Weeks			24 Weeks		
Annualized Rate of Exacerbations	Annualized Rate (95%CI)	1.02 (0.92, 1.15)	1.05 (0.94, 1.17)	1.29 (1.16, 1.43)	NR	NR	NR
	Rate Ratio vs. placebo (95%CI)	0.8 (0.69, 0.93)	0.82 (0.70, 0.95)	reference	NR	NR	NR

All reported p-values are adjusted to address multiplicity across the two doses of brensocatib and the hierarchy of the primary and secondary end points.

95% CI: 95 percent confidence interval, mg: milligram, n: number, N: total number, NR: not reported, NE: not estimable, vs: versus

*Statistical testing for this result was not performed according to the hierarchical testing procedure.

†Unadjusted annualized rate per person-year

‡Not estimable due to low number of exacerbations in both brensocatib arms

§Data come from Insmed data request and are not peer-reviewed

#The reported p values are based on the odds ratios from logistic regression, as prespecified in the statistical analysis plan, because these P values were used in the hierarchical testing.

Table D3.5. Efficacy: Lung Function, Quality of Life, Sputum Biomarker Outcomes

Trial		ASPEN[8,23]			WILLOW[19,23,89]		
Arm		**Brensocatib 10 mg**	**Brensocatib 25 mg**	**Placebo**	**Brensocatib 10 mg**	**Brensocatib 25 mg**	**Placebo**
N		**583**	**575**	**563**	**82**	**87**	**87**
Timepoint		**52 Weeks**			**24 Weeks**		
Lung Function Outcomes							
Post-BDR FEV_1 mL	n evaluated[†]	579	571	563	NR	NR	NR
	LS Mean CFB (SE)	-50 (9)	-24 (10)	-62 (9)	NR	NR	NR
	LS Mean Difference vs. placebo (95%CI); p-value	11 (-14, 37); p=0.38	38 (11, 65); p=0.04	reference	NR	NR	NR
Post-BDR FEV_1 % Predicted	n evaluated[†]	NR	NR	NR	77	77	73
	LS Mean CFB (SE)	NR	NR	NR	-0.3 (0.9)	-0.3 (0.8)	-1.8 (0.9)
	LS Mean Difference vs. placebo (95%CI); p-value	NR	NR	NR	1.5 (-0.7, 3.6); NR	1.5 (-0.7, 3.6); NR	reference
Post-BDR FVC	n evaluated[†]	564	551	539	NR	NR	NR
	LS Mean CFB (SE), mL	-51 (12)	-12 (13)	-87 (12)	NR	NR	NR
	Difference vs. placebo (95%CI); p-value	36 (3, 69); NR	75 (40, 110); NR	reference	NR	NR	NR
Quality of Life-Bronchiectasis Questionnaire Domain Scores (QoL-B)[‡§]							
Respiratory Symptom	n evaluated[†]	487	495	486	75	77	72
	at Baseline, Mean (SD)	59.8 (17.0)	61.9 (17.2)	60.0 (16.8)	NR	NR	NR
	LS Mean CFB (SE)	6.84 (0.77)	8.58 (0.76)	4.81 (0.75)	3.8 (0.78)	5.9 (0.76)	5.7 (0.77)
	LS Mean Difference vs. placebo (95%CI); p-value	2.03 (-0.08, 4.14); NA*	3.77 (1.68, 5.85); NA*	reference	-2.0 (-3.9, 0.02); NR	0.2 (-1.8, 2.2); NR	Reference
Physical Functioning	LS Mean Difference vs. placebo (95%CI)	NR	NR	NR	4.5 (1.84, 7.06)	4.8 (2.24, 7.44)	Reference
Role Functioning	LS Mean Difference vs. placebo (95%CI)	NR	NR	NR	0.7 (-1.58, 2.90)	1 (-1.27, 3.20)	Reference
Emotional Functioning	LS Mean Difference vs. placebo (95%CI)	NR	NR	NR	1.4 (-0.59, 3.36)	5.1 (3.12, 7.07)	Reference

Trial		ASPEN[8,23]			WILLOW[19,23,89]		
Arm		Brensocatib 10 mg	Brensocatib 25 mg	Placebo	Brensocatib 10 mg	Brensocatib 25 mg	Placebo
N		583	575	563	82	87	87
Timepoint		52 Weeks			24 Weeks		
Social Functioning	LS Mean Difference vs. placebo (95%CI)	NR	NR	NR	-2.5 (-5.01, 0.09)	-2.4 (-4.95, 0.14)	Reference
Vitality	LS Mean Difference vs. placebo (95%CI)	NR	NR	NR	1.6 (-0.80, 4.08)	3 (0.59, 5.46)	Reference
Health Perceptions	LS Mean Difference vs. placebo (95%CI)	NR	NR	NR	2.5 (0.15, 4.93)	3.3 (0.92, 5.69)	Reference
Treatment Burden	LS Mean Difference vs. placebo (95%CI)	NR	NR	NR	NE	NE	Reference
Other Quality of Life Measures[§]							
LCQ Physical	LS Mean Difference vs. placebo (95%CI)	NR	NR	NR	0.1 (-0.07, 0.18)	0 (-0.14, 0.11)	Reference
LCQ Psychological	LS Mean Difference vs. placebo (95%CI)	NR	NR	NR	0 (-0.14, 0.17)	0 (-0.12, 0.19)	Reference
LCQ Social	LS Mean Difference vs. placebo (95%CI)	NR	NR	NR	-0.1 (-0.23, 0.09)	0.1 (-0.01, 0.30)	Reference
LCQ Total	LS Mean Difference vs. placebo (95%CI)	NR	NR	NR	0 (-0.40, 0.41)	0.2 (-0.24, 0.57)	Reference
SGRQ Symptoms Score	LS Mean Difference vs. placebo (95%CI)	NR	NR	NR	-1.0 (-5.92, 4.0)	0.6 (-4.68, 5.81)	Reference
Daily BEST Score	n evaluated[†]	558	556	549	NR	NR	NR
	LS Mean CFB (SE)	-0.59 (0.08)	-0.99 (0.09)	-0.43 (0.09)	NR	NR	NR
	Difference vs. placebo; p-value	-0.17 (-0.41, 0.07); NR	-0.57 (-0.83, -0.32); NR	reference	NR	NR	NR
Sputum Neutrophil Elastase							
Sputum Neutrophil Elastase	Mean Change (log_{10} mcg/mL)	NR	NR	NR	-0.9 (-1.1, -0.8)#	-1.0 (-1.2, -0.8)#	-0.1 (-0.3, 0)#

All reported p-values are adjusted to address multiplicity across the two doses of brensocatib and the hierarchy of the primary and secondary end points.
95% CI: 95 percent confidence interval, BDR: bronchodilator, BEST: Bronchiectasis Exacerbation and Symptoms Tool, CFB: change from baseline, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, LCQ: Leicester Cough Questionnaire, LS: least squares, mcg: microgram, mg: milligram, mL: milliliter, n: number, N: total number, NR: not reported, QoL-B: Quality of Life-Bronchiectasis questionnaire, SD: standard deviation, SE: standard error, SQRG: St. George's Respiratory Questionnaire, NE: not estimable

* Statistical testing for this result was not performed according to the hierarchical testing procedure.

† Participants without baseline data or complete measurements were excluded as baseline values were covariates and adjusted for.

‡ QOL-B RSS questionnaire was administered to adult patients only, and scores were not available for 78 of 566 adults in the 10-mg brensocatib group, 62 of 559 adults in the 25-mg brensocatib group, and 68 of 555 adults in the placebo group.

§ Positive least squares mean differences indicate an improvement with brensocatib versus placebo.

Data digitized from figures, interpret with caution.

Table D3.6. Subgroup Efficacy: Rate of Exacerbations at 52 Weeks

Trial		ASPEN[8]				
Arm(s)		Brensocatib 10 mg	Brensocatib 25 mg	Placebo	Brensocatib 10 mg vs. Placebo	Brensocatib 25 mg vs. Placebo
Outcome		n (%)	n (%)	n (%)	Rate Ratio (95%CI)	Rate Ratio (95%CI)
Overall		**583 (100.0)**	**575 (100.0)**	**563 (100.0)**	**0.79 (0.68, 0.92)***	**0.81 (0.69, 0.94)***
Age	12 to <18 years	17 (2.9)	16 (2.8)	8 (1.4)	0.41 (0.11, 1.58)	0.73 (0.20, 2.68)
	18 to <65 years	281 (48.2)	257 (44.7)	295 (52.4)	0.81 (0.66, 0.99)*	0.70 (0.57, 0.86)*
	≥65 years	266 (45.6)	302 (52.5)	260 (46.2)	0.79 (0.63, 0.99)*	0.93 (0.74, 1.15)
	<75 years	482 (82.7)	491 (85.4)	470 (83.5)	0.81 (0.69, 0.95)*	0.79 (0.68, 0.93)*
	≥75 years	82 (14.1)	84 (14.6)	93 (16.5)	0.61 (0.40, 0.94)*	0.89 (0.59, 1.34)
	≥18 years	547 (93.8)	559 (97.2)	555 (98.6)	0.80 (0.69, 0.93)*	0.80 (0.69, 0.93)*
Sex	Female	371 (63.6)	360 (62.6)	362 (64.3)	0.81 (0.68, 0.96)*	0.83 (0.70, 1.00)
	Male	193 (33.1)	215 (37.4)	201 (35.7)	0.75 (0.57, 0.99)*	0.75 (0.57, 0.98)*
Race	American Indian or Alaska Native	8 (1.4)	6 (1.0)	9 (1.6)	NE	NE
	Asian	63 (10.8)	64 (11.1)	64 (11.4)	0.40 (0.23, 0.67)*	0.41 (0.24, 0.70)
	Black or African American	1 (0.2)	5 (0.9)	3 (0.5)	NE	NE
	Native Hawaiian or Other Pacific Islander	1 (0.2)	0 (0.0)	1 (0.2)	NE	NE
	White	416 (71.4)	430 (74.8)	405 (71.9)	0.79 (0.67, 0.94)*	0.79 (0.67, 0.93)*
	Other	14 (2.4)	13 (2.3)	11 (2.0)	NE	NE
Ethnicity	Hispanic or Latino	171 (29.3)	164 (28.5)	170 (30.2)	0.94 (0.70, 1.26)	0.92 (0.69, 1.24)
	Not Hispanic or Latino	378 (64.8)	397 (69.0)	373 (66.3)	0.73 (0.61, 0.87)*	0.77 (0.64, 0.92)*
Number of PEs in Prior 12 Months	2	395 (67.8)	412 (71.7)	396 (70.3)	0.73 (0.60, 0.89)*	0.78 (0.65, 0.95)*
	≥3	169 (29.0)	163 (28.3)	167 (29.7)	0.89 (0.72, 1.11)	0.85 (0.67, 1.07)
Chronic Use of Antibiotics	Yes	141 (24.2)	154 (26.8)	133 (23.6)	0.76 (0.59, 0.97)*	0.74 (0.57, 0.96)*
	No	423 (72.6)	421 (73.2)	430 (76.4)	0.80 (0.66, 0.96)*	0.82 (0.68, 0.98)*
Maintenance Use of Macrolides	Yes	106 (18.2)	114 (19.8)	105 (18.7)	0.79 (0.58, 1.06)	0.79 (0.58, 1.08)
	No	458 (78.6)	461 (80.2)	458 (81.3)	0.78 (0.66, 0.93)*	0.80 (0.67, 0.95)*

Trial		ASPEN[8]				
Arm(s)		Brensocatib 10 mg	Brensocatib 25 mg	Placebo	Brensocatib 10 mg vs. Placebo	Brensocatib 25 mg vs. Placebo
Outcome		n (%)	n (%)	n (%)	Rate Ratio (95%CI)	Rate Ratio (95%CI)
Overall		**583 (100.0)**	**575 (100.0)**	**563 (100.0)**	**0.79 (0.68, 0.92)***	**0.81 (0.69, 0.94)***
***P. aeruginosa* Colonization Status**	Positive	199 (34.1)	205 (35.7)	199 (35.3)	0.75 (0.59, 0.95)*	0.88 (0.70, 1.10)
	Negative	365 (62.6)	370 (64.3)	364 (64.7)	0.81 (0.67, 0.98)*	0.77 (0.64, 0.94)*
Bronchiectasis Severity Index Score	≤4	131 (22.5)	150 (26.1)	148 (26.3)	0.77 (0.55, 1.07)	0.69 (0.50, 0.95)*
	5-8	270 (46.3)	239 (41.6)	220 (39.1)	0.71 (0.56, 0.89)*	0.77 (0.60, 0.97)*
	≥9	163 (28.0)	182 (31.7)	195 (34.6)	0.92 (0.72, 1.17)	0.92 (0.73, 1.17)
	<Median	277 (47.5)	278 (48.3)	275 (48.8)	0.77 (0.61, 0.97)*	0.74 (0.59, 0.92)*
	≥Median	287 (49.2)	293 (51.0)	288 (51.2)	0.80 (0.66, 0.97)*	0.86 (0.70, 1.04)
Bronchiectasis Computed Tomography Score	<Median	266 (45.6)	273 (47.5)	255 (45.3)	0.78 (0.62, 0.98)*	0.91 (0.73, 1.14)
	≥Median	298 (51.1)	302 (52.5)	308 (54.7)	0.81 (0.67, 0.98)*	0.74 (0.61, 0.91)*
Post-Bronchodilator FEV_1 (% Predicted)	<50%	98 (16.8)	102 (17.7)	98 (17.4)	1.01 (0.70, 1.46)	1.23 (0.86, 1.75)
	≥50%	466 (79.9)	469 (81.6)	465 (82.6)	0.74 (0.62, 0.87)*	0.72 (0.61, 0.85)*
Stratification Region	North America	79 (13.6)	83 (14.4)	81 (14.4)	0.66 (0.45, 0.97)*	0.83 (0.59, 1.18)
	Europe	223 (38.3)	221 (38.4)	221 (39.3)	0.90 (0.72, 1.14)	0.86 (0.70, 1.08)
	Japan	30 (5.1)	28 (4.9)	29 (5.2)	0.37 (0.16, 0.87)*	0.32 (0.14, 0.75)*
	Rest of World	232 (39.8)	243 (42.3)	232 (41.2)	0.79 (0.63, 0.99)*	0.83 (0.65, 1.06)
Geographic Region	South America	169 (29.0)	157 (27.3)	157 (27.9)	0.91 (0.68, 1.23)	0.92 (0.67, 1.26)
	Eastern Europe	74 (12.7)	68 (11.8)	72 (12.8)	0.54 (0.29, 0.99)*	0.62 (0.35, 1.08)
	Western countries	206 (35.3)	205 (35.7)	201 (35.7)	0.86 (0.70, 1.07)	0.86 (0.69, 1.06)
	Asian countries	79 (13.6)	91 (15.8)	88 (15.6)	0.62 (0.41, 0.94)*	0.62 (0.41, 0.94)*
	Oceania	36 (6.2)	54 (9.4)	45 (8.0)	0.79 (0.54, 1.17)	0.77 (0.51, 1.18)
Blood Eosinophil Count	≥300/mm^3	110 (18.9)	111 (19.3)	106 (18.8)	0.72 (0.52, 0.99)*	0.86 (0.62, 1.20)
	<300/mm^3	452 (77.5)	461 (80.2)	452 (80.3)	0.81 (0.68, 0.95)*	0.79 (0.67, 0.94)*
Smoking Status	Former smoker	159 (27.3)	163 (28.3)	183 (32.5)	0.83 (0.64, 1.07)	0.75 (0.58, 0.97)*
	Never smoked	405 (69.5)	412 (71.7)	380 (67.5)	0.78 (0.65, 0.93)*	0.84 (0.70, 1.01)
Use of Inhaled Steroids	Yes	314 (53.9)	324 (56.3)	352 (62.5)	0.83 (0.69, 0.99)*	0.76 (0.63, 0.92)*
	No	250 (42.9)	251 (43.7)	211 (37.5)	0.78 (0.60, 1.01)	0.93 (0.73, 1.20)

Trial		ASPEN[8]				
Arm(s)		Brensocatib 10 mg	Brensocatib 25 mg	Placebo	Brensocatib 10 mg vs. Placebo	Brensocatib 25 mg vs. Placebo
Outcome		n (%)	n (%)	n (%)	Rate Ratio (95%CI)	Rate Ratio (95%CI)
Overall		**583 (100.0)**	**575 (100.0)**	**563 (100.0)**	**0.79 (0.68, 0.92)***	**0.81 (0.69, 0.94)***
History of Asthma	Yes	96 (16.5)	109 (19.0)	111 (19.7)	0.96 (0.71, 1.30)	0.99 (0.72, 1.34)
	No	468 (80.3)	466 (81.0)	452 (80.3)	0.75 (0.63, 0.89)*	0.76 (0.64, 0.90)*
History of COPD	Yes	77 (13.2)	83 (14.4)	102 (18.1)	0.70 (0.44, 1.13)	0.81 (0.56, 1.18)
	No	487 (83.5)	492 (85.6)	461 (81.9)	0.80 (0.68, 0.93)*	0.80 (0.68, 0.95)*
Hospitalized in Prior 24 Months for PE	Yes	141 (24.2)	133 (23.1)	142 (25.2)	0.89 (0.68, 1.16)	0.81 (0.61, 1.07)
	No	423 (72.6)	442 (76.9)	421 (74.8)	0.76 (0.63, 0.90)*	0.81 (0.68, 0.96)*

Rate ratios lower than 1.0 indicate improved efficacy with brensocatib over placebo.

95% CI: 95 percent confidence interval, COPD: chronic obstructive pulmonary disease, FEV_1: forced expiratory volume in one second, mg: milligram, mm^3: cubic millimeters, n: number, NE: not estimable, PE: pulmonary exacerbation

*95% confidence intervals do not include 1.0, indicating statistical significance compared to placebo.

Table D3.7. Subgroup Efficacy: Post-Bronchodilator FEV_1 at 52 Weeks

Trial		ASPEN[22]				
Arm(s)		**Brensocatib 10 mg**	**Brensocatib 25 mg**	**Placebo**	**Brensocatib 10 mg vs. Placebo**	**Brensocatib 25 mg vs. Placebo**
Outcome		**n (%)**	**n (%)**	**n (%)**	**LS Mean Difference (95% CI)**	**LS Mean Difference (95% CI)**
Overall		**583 (100.0)**	**575 (100.0)**	**563 (100.0)**	**11 (-14, 37)**	**38 (11, 65)***
Age	12 to <18 years	17 (2.9)	14 (2.4)	8 (1.4)	287 (-134, 707)	324 (-96, 745)
	18 to <65 years	281 (48.2)	243 (42.3)	280 (49.7)	-4 (-43, 35)	31 (-11, 74)
	≥65 years	266 (45.6)	294 (51.1)	251 (44.6)	21 (-12, 55)	42 (9, 75)*
	<75 years	482 (82.7)	470 (81.7)	448 (79.6)	10 (-19, 39)	40 (10, 70)*
	≥75 years	82 (14.1)	81 (14.1)	91 (16.2)	23 (-35, 80)	29 (-26, 83)
	≥18 years	547 (93.8)	537 (93.4)	531 (94.3)	8 (-18, 34)	36 (10, 63)*
Sex	Female	371 (63.6)	342 (59.5)	347 (61.6)	-3 (-32, 26)	32 (2, 62)*
	Male	193 (33.1)	209 (36.3)	192 (34.1)	42 (-9, 94)	50 (-1, 102)
Race	American Indian or Alaska Native	8 (1.4)	6 (1.0)	8 (1.4)	256 (-233, 746)	256 (34, 478)*
	Asian	63 (10.8)	63 (11.0)	58 (10.3)	18 (-27, 63)	69 (24, 114)*
	Black or African American	1 (0.2)	5 (0.9)	2 (0.4)	NE	NE
	Native Hawaiian or Other Pacific Islander	1 (0.2)	0 (0.0)	1 (0.2)	NE	NE
	White	416 (71.4)	409 (71.1)	392 (69.6)	11 (-19, 40)	27 (-4, 58)
	Other	14 (2.4)	13 (2.3)	10 (1.8)	30 (-118, 178)	152 (-96, 399)
Ethnicity	Hispanic or Latino	171 (29.3)	156 (27.1)	164 (29.1)	19 (-36, 75)	29 (-26, 84)
	Not Hispanic or Latino	378 (64.8)	382 (66.4)	355 (63.1)	6 (-23, 35)	40 (9, 70)*
Number of PEs in Prior 12 Months	2	395 (67.8)	392 (68.2)	375 (66.6)	11 (-21, 44)	38 (7, 70)*
	≥3	169 (29.0)	159 (27.7)	164 (29.1)	12 (-30, 55)	35 (-16, 87)
Chronic Use of Antibiotics	Yes	141 (24.2)	147 (25.6)	128 (22.7)	-22 (-75, 30)	40 (-9, 89)
	No	423 (72.6)	404 (70.3)	411 (73.0)	22 (-8, 52)	37 (5, 68)*
	Yes	106 (18.2)	110 (19.1)	104 (18.5)	-15 (-70, 39)	44 (-16, 104)

Trial		ASPEN[22]				
Arm(s)		**Brensocatib 10 mg**	**Brensocatib 25 mg**	**Placebo**	**Brensocatib 10 mg vs. Placebo**	**Brensocatib 25 mg vs. Placebo**
Outcome		**n (%)**	**n (%)**	**n (%)**	**LS Mean Difference (95% CI)**	**LS Mean Difference (95% CI)**
Overall		**583 (100.0)**	**575 (100.0)**	**563 (100.0)**	**11 (-14, 37)**	**38 (11, 65)***
Maintenance Use of Macrolides	No	458 (78.6)	441 (76.7)	435 (77.3)	17 (-12, 47)	35 (2, 73)*
***P. aeruginosa* Colonization Status**	Positive	199 (34.1)	194 (33.7)	190 (33.7)	4 (-32, 39)	40 (2, 78)*
	Negative	365 (62.6)	357 (62.1)	349 (62.0)	16 (-19, 51)	37 (2, 73)*
Bronchiectasis Severity Index Score	≤4	131 (22.5)	144 (25.0)	144 (25.6)	-7 (-68, 54)	23 (-33, 80)
	5-8	270 (46.3)	231 (40.2)	208 (36.9)	23 (-15, 61)	22 (-17, 60)
	≥9	163 (28.0)	176 (30.6)	187 (33.2)	17 (-22, 56)	74 (28, 121)*
	<Median	277 (47.5)	268 (46.6)	261 (46.4)	0 (-40, 40)	18 (-21, 58)
	≥Median	287 (49.2)	283 (49.2)	278 (49.4)	26 (-8, 59)	58 (22, 94)*
Bronchiectasis Computed Tomography Score	<Median	266 (45.6)	261 (45.4)	249 (44.2)	8 (-33, 50)	30 (-13, 72)
	≥Median	298 (51.1)	290 (50.4)	290 (51.5)	17 (-15, 49)	48 (15, 81)*
Post-Bronchodilator FEV_1 (% Predicted)	<50%	98 (16.8)	96 (16.7)	92 (16.3)	-10 (-60, 40)	32 (-23, 87)
	≥50%	466 (79.9)	455 (79.1)	447 (79.4)	16 (-13, 46)	39 (9, 69)*
Stratification Region	North America	79 (13.6)	81 (14.1)	75 (13.3)	20 (-44, 85)	77 (-5, 159)
	Europe	223 (38.3)	211 (36.7)	214 (38.0)	5 (-36, 46)	35 (-8, 78)
	Japan	30 (5.1)	28 (4.9)	29 (5.2)	47 (-20, 115)	97 (32, 162)*
	Rest of World	232 (39.8)	231 (40.2)	221 (39.3)	11 (-32, 54)	20 (-20, 60)
Geographic Region	South America	169 (29.0)	149 (25.9)	151 (26.8)	10 (-46, 67)	13 (-41, 66)
	Eastern Europe	74 (12.7)	65 (11.3)	67 (11.9)	48 (-23, 120)	41 (-50, 131)
	Western countries	206 (35.3)	196 (34.1)	193 (34.3)	1 (-42, 44)	56 (8, 104)*
	Asian countries	79 (13.6)	90 (15.7)	84 (14.9)	-1 (-44, 42)	39 (-4, 82)
	Oceania	36 (6.2)	51 (8.9)	44 (7.8)	28 (-51, 108)	32 (-44, 109)
Blood Eosinophil Count	≥300/mm^3	110 (18.9)	110 (19.1)	101 (17.9)	0 (-57, 57)	43 (-24, 110)

Trial		ASPEN[22]				
Arm(s)		Brensocatib 10 mg	Brensocatib 25 mg	Placebo	Brensocatib 10 mg vs. Placebo	Brensocatib 25 mg vs. Placebo
Outcome		n (%)	n (%)	n (%)	LS Mean Difference (95% CI)	LS Mean Difference (95% CI)
Overall		**583 (100.0)**	**575 (100.0)**	**563 (100.0)**	**11 (-14, 37)**	**38 (11, 65)***
	<300/mm^3	452 (77.5)	438 (76.2)	434 (77.1)	16 (-13, 46)	37 (7, 66)*
Smoking Status	Former smoker	159 (27.3)	159 (27.7)	177 (31.4)	11 (-33, 55)	51 (8, 93)*
	Never smoked	405 (69.5)	392 (68.2)	362 (64.3)	12 (-20, 44)	33 (-1, 66)
Use of Inhaled Steroids	Yes	314 (53.9)	312 (54.3)	337 (59.9)	13 (-21, 47)	41 (6, 76)*
	No	250 (42.9)	239 (41.6)	202 (35.9)	10 (-29, 49)	37 (-4, 78)
History of Asthma	Yes	96 (16.5)	105 (18.3)	106 (18.8)	-23 (-89, 42)	24 (-41, 90)
	No	468 (80.3)	446 (77.6)	433 (76.9)	20 (-8, 48)	42 (12, 71)*
History of COPD	Yes	77 (13.2)	80 (13.9)	96 (17.1)	10 (-45, 65)	39 (-12, 90)
	No	487 (83.5)	471 (81.9)	443 (78.7)	10 (-19, 39)	37 (7, 67)*
Hospitalized in Prior 24 Months for PE	Yes	141 (24.2)	130 (22.6)	134 (23.8)	58 (4, 113)*	110 (53, 166)*
	No	423 (72.6)	421 (73.2)	405 (71.9)	-3 (-32, 26)	15 (-15, 44)

Least squares mean differences greater than 0 indicate improved efficacy with brensocatib over placebo.

95% CI: 95 percent confidence interval, COPD: chronic obstructive pulmonary disease, FEV_1: forced expiratory volume in one second, mg: milligram, mm^3: cubic millimeters, n: number, NE: not estimable, PE: pulmonary exacerbation

*95% confidence intervals do not include 0, indicating statistical significance compared to placebo.

Table D3.8. Safety

Trial		ASPEN[8]			WILLOW[19]		
Arm		**Brensocatib 10 mg**	**Brensocatib 25 mg**	**Placebo**	**Brensocatib 10 mg**	**Brensocatib 25 mg**	**Placebo**
N		**582**	**574**	**563**	**81**	**89**	**85**
Adverse Events	Any	452 (77.7)	440 (76.7)	448 (79.6)	75 (93)	74 (83)	67 (79)
	Excluding exacerbations	NR	NR	NR	51 (63)	48 (54)	32 (38)
	Serious	101 (17.4)	97 (16.9)	108 (19.2)	11 (14)	10 (11)	19 (22)
	Severe	74 (12.7)	67 (11.7)	90 (16.0)	3 (4)	6 (7)	13 (15)
	Treatment-related	72 (12.4)	85 (14.8)	73 (13.0)	NR	NR	NR
	Serious-related	0	1 (0.2)	0	NR	NR	NR
Mortality	Overall	NR	NR	NR	0	1 (1)†	0
	due to AEs	3 (0.5)	4 (0.7)	7 (1.2)	0	1 (1)†	0
Treatment Discontinuation	Overall	NR	NR	NR	NR	NR	NR
	due to AEs	25 (4.3)	22 (3.8)	23 (4.1)	6 (7)	6 (7)	9 (11)
Study Discontinuation	Overall	78 (13.4)	65 (11.3)	75 (13.3)	6 (6.9)	12 (13.8)	13 (14.9)
	due to AEs	14 (2.4)	16 (2.8)	16 (2.8)	3 (4)	4 (4)	3 (4)
Adverse Events of Special Interest*							
Any AE of Special Interest		42 (7.2)	56 (9.8)	53 (9.4)	27 (33)	35 (39)	23 (27)
Skin Event		NR	NR	NR	12 (15)	21 (24)	10 (12)
Hyperkeratosis		8 (1.4)	17 (3.0)	4 (0.7)	3 (3.7)	1 (1.1)	0‡
Periodontitis/gingivitis		8 (1.4)	12 (2.1)	15 (2.7)	13 (16)§	9 (10)§	3 (4)§
Infection		NR	NR	NR	11 (14)	15 (17)	15 (18)
Severe Infection		4 (0.7)	7 (1.2)	4 (0.7)	NR	NR	NR
Pneumonia		23 (4.0)	27 (4.7)	33 (5.9)	0	3 (3.4)	1 (1.2)
Common Adverse Events							
COVID-19		92 (15.8)	120 (20.9)	89 (15.8)	NR	NR	NR
Nasopharyngitis		45 (7.7)	36 (6.3)	43 (7.6)	NR	NR	NR
Cough		41 (7.0)	35 (6.1)	36 (6.4)	15 (19)	12 (13)	10 (12)
Headache		39 (6.7)	49 (8.5)	39 (6.9)	8 (10)	12 (13)	3 (4)

Trial	ASPEN[8]			WILLOW[19]		
Arm	**Brensocatib 10 mg**	**Brensocatib 25 mg**	**Placebo**	**Brensocatib 10 mg**	**Brensocatib 25 mg**	**Placebo**
N	**582**	**574**	**563**	**81**	**89**	**85**
Bronchiectasis	NR	NR	NR	5 (6)	4 (4)	9 (11)
Diarrhea	26 (4.5)	21 (3.7)	27 (4.8)	5 (6)	3 (3)	9 (11)
Dyspnea	NR	NR	NR	3 (4)	9 (10)	2 (2)
Sputum Increase	NR	NR	NR	9 (11)	9 (10)	6 (7)
Common Serious Adverse Events						
Bronchiectasis	47 (8.1)	48 (8.4)	67 (11.9)	5 (6)	4 (4)	9 (11)
Pneumonia	11 (1.9)	13 (2.3)	16 (2.8)	0	4 (4)	3 (4)

Units are n (%) unless otherwise specified.

AEs: adverse events, mg: milligram, n: number, N: total number, NR: not reported

*An event known to be related to treatment with DPP1-inhibition. Near complete absence of DPP-1 leads to Papillon Lefèvre syndrome that is characterized by gingival hyperplasia and hyperkeratosis

†Due to bronchiectasis progression

‡One participant in the placebo group experienced hyperkeratosis which was not reported as an adverse event of special interest by the investigator

§Dental event

D4. Ongoing Studies

There were no ongoing studies of brensocatib for non-cystic fibrosis bronchiectasis at the time of our review. However, an expanded access study (NCT05344508) is available for participants who have successfully completed the ASPEN trial to gain early access to brensocatib 10 mg oral tablets once daily.

D5. Previous Systematic Reviews and Technology Assessments

We identified one health technology assessments (HTA) of brensocatib for the treatment of non-cystic fibrosis bronchiectasis initiated by the National Institute for Health and Care Excellence (NICE). No systematic reviews comparing brensocatib to other existing therapies for bronchiectasis were identified at the time of our review.

NICE Technology Assessment for Brensocatib [ID6448]

NICE initiated a health technology assessment assessing brensocatib for the treatment of moderate to severe non-cystic fibrosis bronchiectasis in people 12 years and over. The topic was selected in May 2024 and information on the scope of the review was not yet available at the time of our review.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1.1. Impact Inventory

Sector	Type of Impact (Add Additional Domains, as Relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if Quantified), Likely Magnitude & Impact (if Not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	-	-	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	X	X	
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

The "X" within the table shows that the domain was included in the analysis. The square in the table represents a potentially applicable domain that was not included in the analysis. Adapted from Sanders et al[93]

Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[94]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps 3 and 4.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

Target Population

The population for the economic evaluation included adults with NCFB who had 2 or more exacerbations at baseline. The target population matched the ASPEN brensocatib phase III clinical trial population.[95] Baseline characteristics for our model inputs are the weighted average of the patient characteristics across the brensocatib 25 mg, brensocatib 10 mg, and placebo groups of the trial. (Table E1.2)

Table E1.2. Base-Case Model Cohort Characteristics*

	Value	Primary Source
Mean Age, Years	59.8	Chalmers, 2024 [95]
Female, n (%)	63.45%	Chalmers, 2024 [95]
2 Exacerbations in Prior 12 Months, %	70.83%	Chalmers, 2024 [95]
≥3 Exacerbations in Prior 12 Months, %	29.17%	Chalmers, 2024 [95]
Pseudomonas Aeruginosa Culture Status Positive, n (%)	35%	Chalmers, 2024 [95]

Treatment Strategies

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The full list of interventions is as follows: Brensocatib 25 mg per day plus current Usual Care – Base Case

- Brensocatib 10 mg per day plus current Usual Care – Scenario Analysis Only

Comparators

Brensocatib plus current Usual Care for NCFB was compared to Usual Care alone for NCFB (represented by the placebo arm in the ASPEN trial). Current Usual Care includes regular physician follow up and antibiotics, mucolytics, pulmonary rehabilitation, and airway clearance devices used as needed and as indicated.

E2. Model Inputs and Assumptions

Key model assumptions can be found in Table 4.1 and key model inputs can be found in Table 4.2.

Model Assumptions

Table E2.1. Model Assumptions

Assumption	Rationale
Model Structure	
The risk of exacerbation is higher in individuals with PsA or NTM infections compared to those with NCFB without chronic infection. However, the risk of the onset of chronic infection or rate of eradication are assumed to remain consistent across both exacerbated and non-exacerbated states.	Clinical symptoms of NCFB are likely to worsen with chronic infection. Therefore, patients with PsA and NTM have a higher chance of having pulmonary exacerbation. Exacerbation is unlikely to modify the risk of having chronic infection. Currently, there is limited data on how exacerbations influence the onset or eradication of PsA and NTM infections.

Assumption	Rationale
Treatment discontinuation from adverse events (AEs) was reflected only in the treatment cost calculation.	Our model used inputs from the intention-to-treat analysis of the ASPEN trial.[8] Thus, the overall treatment efficacy includes patients who both continue and discontinue from treatment. Treatment discontinuation decreased the overall pharmacy cost of drug therapy, so the total costs of therapy were adjusted to reflect the proportion of patients who remain on therapy in the clinical trial.
Lung transplantation and antimicrobial resistance were not considered in the model.	Lung transplantation and antimicrobial resistance may impact the prognosis of NCFB. However, there is insufficient evidence from trial data that brensocatib reduces MRSA infection or the need for lung transplantation, relative to comparator treatment. Additionally, the overall proportion of the target population affected by lung transplantation would be extremely small.
Clinical Efficacy Data	
Brensocatib efficacy data (rate of pulmonary exacerbations) were based on the results from 25 mg once daily arm of the ASPEN trial.	While the primary outcome was similar in both 10 mg and 25 mg doses, brensocatib 25 mg showed statistically significant less decrease in forced expiratory volume compared with placebo while the 10 mg dose was not statistically significant.
Adverse events (AEs) only impact treatment discontinuation. No impact of AEs on costs or outcomes were modeled.	The proportion of individuals who experienced adverse events was similar between treatment and placebo groups. Thus, we did not incorporate AE-related costs or disutilities into the model.
A special medical attention for an exacerbation would not continue for more than one cycle for most of the patients with exacerbation.	According to expert opinion, most patients receive special attention and care beyond usual care for a week to a month following an exacerbation. After one month, we assumed that usual care with or without brensocatib would suffice for a 90% of those with exacerbation
The proportion of severe exacerbations leading to hospitalization out of all exacerbation is similar between Brensocatib and Usual Care, while the overall rate of pulmonary exacerbations is lower with Brensocatib.	Although the point estimate of the annualized rate of severe exacerbations was lower with brensocatib compared to placebo from the ASPEN clinical trial, the confidence intervals for the two groups overlap. For the base-case simulation, we assume no difference in the proportion of severe exacerbations among all pulmonary exacerbations. The impact of the changing the risk ratio of severe exacerbation among all exacerbation for Brensocatib versus Usual Care was tested as part of the one-way sensitivity analysis.
Costs and Resource Use	

Assumption	Rationale
Brensocatib will be added-on to Usual Care.	The proportion of participants requiring usual care—comprising physician visits, antibiotics, mucolytics, and airway clearance—was similar at baseline. Brensocatib demonstrated clinical benefits by reducing the rate of exacerbations. However, this reduction does not eliminate the need for ongoing symptom management with standard care while patients remain in the non-exacerbated NCFB state, even when receiving brensocatib as an adjunct therapy.
Utility	
Multiplicative utility functions were used to calculate some health state utilities.	If more than one health attribute are combined into a single health state (e.g. PsA infection and exacerbation), the utility for the health state was calculated as the product of the utilities of individual health attributes. [39] For example, assigned utility weight for the patients with exacerbation while they suffer from chronic PsA infection was calculated from the following approach: Utility weight for NCFB × proportional utility of PsA × proportional utility of exacerbation

Model Inputs

Clinical Inputs

Transition Probabilities

In the base-case, treatment efficacy was modeled by using a differential rate for exacerbations and chronic PsA or NTM infections. Transition probabilities were identified from the ASPEN clinical trial and a systematic review of the literature.[8] Identified risks and incidence rates were converted to 1-month probabilities. Relative risk estimates were used to modify the probability of transitioning from one health state to another. When transitioning from a state without chronic infection or exacerbation to one with both chronic infection and exacerbation, a joint probability of each event

was used to calculate the transition probability. The transition probabilities used in the model are listed in Table E2.2 and 2.3.

Table E2.2. 1-Month Transition Probabilities to Exacerbation and Chronic Infection for Brensocatib and Placebo

	Brensocatib 25 mg	Placebo	Source
Incidence of Exacerbation (1 Month)*	0.0870	0.1075	Chalmers, 2025[8]
Risk Ratio for Exacerbation Brensocatib vs. Usual Care	0.81		Chalmers, 2025[8]
Risk Ratio of Exacerbation PsA vs. No PsA NCFB	1.14		Chalmers, 2025; Araújo, 2018[8,49]
Risk Ratio of Exacerbation NTM vs. No NTM NCFB	1.14		Assumption and Expert Opinion
Incidence of PsA Infection (1 Month)	0.0022	0.0025	Chalmers, 2025; Aksamit, 2024[8,41]
Incidence of NTM Infection (1 Month)	0.0029	0.0034	Chalmers, 2025, Aksamit, 2024[8,41]
Risk Ratio of PsA or NTM Infection Brensocatib vs. Usual Care	0.78†		Chalmers, 2025[8]
Risk Ratio of hospital admission (severe exacerbation) if exacerbation is incurred, Brensocatib vs. Usual Care	1		Chalmers, 2025[8]

NCFB: Non-Cystic Fibrosis Bronchiectasis, NTM: Non-tuberculous mycobacteria, PsA: Pseudomonas Aeruginosa, VS: versus

*The 1-month probabilities were calculated from the 1-year probability available from ASPEN trial report

†Derived from the rates of infection or infestation. The overall infection rates of 4.0% for brensocatib 25 mg versus 5.2% for placebo.

‡A risk ratio range of 0.93 – 1 was tested using a one-way sensitivity analysis. In the model analysis plan, we proposed a scenario analysis.

Table E2.3. 1-Month Transition Probabilities for Resolution of Exacerbation and Chronic Infection

	Transition Probability	Source
From Exacerbation to NCFB	0.900	Barker, 2025 and expert opinion[96]
From PsA Infection to NCFB	0.053*	Conceição, 2024[97]
From NTM Infection to NCFB	0.049†	Kwak, 2019[98]

NCFB: Non-Cystic Fibrosis Bronchiectasis, NTM: Non-tuberculous mycobacteria, PsA: Pseudomonas Aeruginosa

*Calculated from 12-month PsA eradication rate of 48% on a constant rate of eradication over time.

†Calculated from 12-month 45.6% treatment success rate from a recent meta-analysis on a constant success rate over time

Mortality

The mortality rate from each health state was derived from the US life table for the general population and adjusted using mortality risk ratios specific to each condition, relative to either the general population or baseline NCFB. For the health states with chronic infection and exacerbation, the model used the product of the base mortality rate and the condition-specific rate ratio (RR) as an input. For example, patients with NCFB exacerbation with PsA infection, the state specific per cycle mortality was "all-cause mortality × RR for NCFB vs. all-cause × RR for NCFB with Exacerbation vs. NCFB × RR for PsA infection vs. No PsA infection."

Table E2.5. Mortality Inputs

Parameter	Value	Source
All-Cause Mortality	Weighted average of male-female age specific mortality rate	2019 US Life Table[99]
Rate Ratios		
NCFB vs. All-Cause	1.77	Shoaib, 2025[14]
NCFB with Exacerbation vs. NCFB	1.16	Chalmers, 2018[40]
PsA Infection vs. No PsA Infection	1.47	Jacobs, 2020[100]
NTM Infection vs. No NTM Infection*	1.47	Park, 2019; Aksamit, 2024; Wang, 2023[41,101,102], Expert opinion

CI: Confidence Interval; HR: Hazard Ratio; NCFB: Non-Cystic Fibrosis Bronchiectasis; NTM: Non-tuberculous mycobacteria; PsA: Pseudomonas Aeruginosa

*Mortality rate varied by study. Per expert opinion, impact of NTM on mortality would be similar to mortality effect observed with PsA infection versus no PsA infection.

Discontinuation

Patients received Brensocatib or current Usual Care until the occurrence of a severe adverse event or complication leading to premature death. As described in Table E2.1., Model Assumptions, the model used data from the intention-to-treat analysis of the ASPEN trial to model treatment discontinuation.[8] Therefore, we assumed that discontinuation did not affect overall treatment efficacy, but treatment costs were adjusted to reflect discontinuation.

Table E2.6. Proportion of Treatment Discontinuation due to AEs

Health State	Brensocatib 10 mg	Brensocatib 25 mg	Placebo
Treatment Discontinuation, %	4.3	3.8	4.1

Adverse Events

Brensocatib and Usual Care were generally well tolerated in clinical trials, with no clinically meaningful differences in the safety profiles between the brensocatib and placebo groups.[8] Further, most adverse events were managed by stopping brensocatib, without direct treatment of the adverse event. Thus, the impact of adverse events on health-related quality of life and costs would be non-differential between the Brensocatib and Usual Care strategies. Since our model used inputs from the intention-to-treat analysis of the ASPEN trial that includes overall treatment effect of discontinuation due to adverse events, we did not specifically include adverse events as a model input.

Heterogeneity and Subgroups

Heterogeneous treatment effects across subgroups were tested using scenario analysis. We used the effect of treatment selection on the rate of exacerbation stratified by presence of chronic PsA infection at baseline and the number of exacerbations in prior 12 months. PsA culture status at the time of clinical trial enrollment was used to determine chronic PsA infection and was categorized as positive or negative. The number of exacerbations in the prior 12 months was categorized as 2 or ≥3. Input values were calculated from the recent pivotal clinical trial.[8] Table E2.7A and E2.7B are the model inputs for testing the heterogeneity across the PsA infection status and baseline exacerbation frequency, respectively.

Table E2.7A. Risk/Rate of Exacerbations per Cycle Stratified by Sputum PsA Culture Status at Baseline

PsA Culture Status	PsA Positive		PsA Negative	
	Brensocatib 25 mg	Placebo	Brensocatib 25mg	Placebo
Rate of Exacerbation	1.54	1.75	0.79	1.04
Risk Ratio	0.88	Ref.	0.77	Ref.

PsA: Pseudomonas Aeruginosa

Note: Trial reported rate ratios. Rate of exacerbation in each subgroup was calculated from the ASPEN clinical trial data using simultaneous linear equations.

Table E2.7B. Risk/Rate of Exacerbations per Cycle Stratified by the Number of Exacerbations in Prior 12 Months

Baseline Exacerbations	2		3 or More	
	Brensocatib 25 mg	Placebo	Brensocatib 25 mg	Placebo
Rate of Exacerbation	0.78	1.07	1.54	1.82
Risk Ratio	0.73	Ref.	0.85	Ref.

Note: Trial reported rate ratios. Rate of exacerbation in each subgroup was calculated from the ASPEN clinical trial data using simultaneous linear equations.

Utilities

Health state utilities for each Markov state were obtained and calculated from a targeted systematic review of publicly available literature.

The Quality of Life-Bronchiectasis questionnaire Respiratory Symptom Domain score (QOL-B RSS) was utilized to measure the patient-reported outcomes for the ASPEN clinical trial.[8] However, algorithms to convert QOL-B RSS to EQ-5D, a health state preference instrument for utility estimation, are not available, limiting the feasibility of using QOL-B RSS for the QALY and evLY calculations. Thus, we calculated utility scores from an alternative disease-specific quality of life measure for each modeled health state. The St George's Respiratory Questionnaire (SGRQ) is a widely accepted disease specific QoL measure for respiratory conditions including bronchiectasis.[50-53] EQ-5D utility was calculated from the SGRQ score using mapping algorithms identified through a targeted review. [54,55] SGRQ scores associated with PsA infection, NTM infection, and exacerbation are also available from published literature.[15,40,103] The published algorithm to calculate the utility weight from SGRQ total score is shown below.[54]

$$Utility\ Weight = 0.9617 - 0.0013\ SGRQ - 0.0001 \times SGRQ^2 + 0.0231 \cdot maleUtility$$

To account for the decrease in the utility score for exacerbation or chronic infection, we applied the utility of these complications as a proportion of the overall utility weight for NCFB (0.719). Additional decreases in the health utility were applied for the subset of patients who require hospitalization (i.e., severe exacerbation) by multiplying an additional proportional multiplicative utility weight of 0.905 to the utility of those with exacerbation.[44]

We calculated and used multiplicative utilities to adjust utilities for patients with exacerbation, chronic PsA and/or NTM infection, and hospitalization.[39] For example, the utility of the health state involving NCFB with both exacerbation and PsA infection was calculated as the product of the baseline utility of NCFB (0.719), the proportional utility of exacerbation relative to NCFB (0.758),

and the proportional utility of PsA infection relative to NCFB (0.699), resulting in a utility of 0.381 for the NCFB with PsA infection and exacerbation health state.

Table E2.8. Health State Utilities

Parameter	(Proportional) Utility Weight	Calculated Utility	Source
NCFB	0.719		Chalmers, 2018[40]
Exacerbation	0.758 of NCFB	0.545	Chalmers, 2018[40]
PsA Infection	0.699 of NCFB	0.503	Chalmers, 2014[15]
NTM Infection	0.699 of NCFB	0.503	Shah, 2021; Jiang, 2021 and expert opinion[42,43]
Severe Exacerbation (Hospital Admission)*	0.905 of exacerbation	0.493	Camac, 2021[44]

NCFB: Non-Cystic Fibrosis Bronchiectasis, NTM: Non-tuberculous mycobacterial, PsA: Pseudomonas Aeruginosa
*Calculation from COPD exacerbation and hospital admission

Results from the ASPEN trial suggest that patients receiving brensocatib experience improvements in quality of life compared to those receiving Usual Care. In our model, we applied differential transition probabilities for patients on Brensocatib versus Usual Care, leading to fewer cases of exacerbation and chronic infection. Therefore, these differences implicitly captured quality of life differences, resulting in a higher overall utility and QALY and evLY gains among patients who received brensocatib compared to placebo.

It remains unclear whether utility benefits extend beyond the drug's impact on reducing exacerbation and infection rates. This uncertainty was explored through scenario analyses. We tested the direct impact of Brensocatib on quality of life via delay in the loss of lung function in a scenario analysis (see Section 2.7 below).

Caregiver Disutilities

A targeted systematic review of the literature was conducted to identify potential impacts of NCFB on caregiver health-related quality of life. There were no studies describing the impact of NCFB on caregivers. Further, there was no evidence presented in the clinical trial that suggests that brensocatib would have an impact on caregiver health-related quality of life. Caregiver burden could be attributed to the difference or changes in the bronchiectasis symptoms and daily functions. According to the ASPEN trial, brensocatib did not introduce a clinically meaningful difference in the BEST (Bronchiectasis exacerbation and symptom tool) score, which would not be translated into a difference in caregiver burden or disutilities between the Brensocatib versus Usual Care. Given these findings, caregiver disutility was not included in the model.

Economic Inputs

All costs used in the model were updated to December 2024 US dollars using Consumer Price Index for Medical care in U.S available from the U.S. Bureau of Labor Statistics. [57]

Drug Costs – Brensocatib

For brensocatib, we used a placeholder price based on net pricing estimates from the manufacturer's earnings call presentation (Q4 2024). The manufacturer indicated that the target price would be in the upper half of between $40K and $96K annually. Calculating the midpoint of the upper half as a target, the monthly cost of brensocatib as a placeholder price for our model is $6,833 ($82,000 annually). We used the same cost inputs for both brensocatib 25mg (base case) and 10mg (scenario).

Severe Exacerbation Costs

Costs associated with severe exacerbation leading to hospitalization were identified through a review of existing literature and previously published economic analyses focused on hospitalization costs among NCFB patients who experienced exacerbations. The exacerbation-related hospitalization costs were applied to a proportion of patients with severe exacerbation (14.7% of all exacerbations). Exacerbation without a need for hospital admission was not a subject of applying severe exacerbation costs.

Table E2.9. Costs of Hospital Admission for Severe Exacerbation

Event	Costs per Encounter	Source
Hospital Admission for Severe Exacerbation	$24,538	Tkacz, 2024[46]

Current Usual Care Costs

Current Usual Care includes any direct costs associated with management of NCFB, including regular physician office visits, outpatient medication (antibiotics and mucolytics), and other supporting services as needed (pulmonary rehabilitation or airway clearance). These costs were accounted for as the baseline cost for the comparator and brensocatib arms. Cost estimates were identified from a targeted literature review. Inputs are presented in Table E2.10.

Table E2.10. Monthly Cost of NCFB, Including Current Usual Care

Markov States	Monthly Cost	Source
NCFB	$ 131: Outpatient physician visits: $52 Outpatient pharmacy: $66 Other support: $12	Tkacz, 2024[46]
Exacerbation, Extra Care in Addition to the Usual Care but Excluding Inpatient Admission	$ 1,010: Outpatient physician visits: $41 Outpatient pharmacy: $83 Acute care: $885	Tkacz, 2024[46]
PsA Infection*	$ 3,097	Blanchette, 2017[47]
NTM Infection*	$ 4,457	Marras, 2018[48]

NCFB: Non-Cystic Fibrosis Bronchiectasis, NTM: Non-tuberculous mycobacteria, PsA: Pseudomonas Aeruginosa
*Costs of PsA infection and NTM infection is not inclusive of exacerbation. Costs of exacerbation were applied on top of PsA and NTM infection costs for the exacerbation + chronic infection states.

Unrelated Healthcare Costs

In addition to the direct costs associated with bronchiectasis and related conditions, we incorporated future unrelated healthcare costs. These included the general healthcare costs incurred by the surviving population, irrespective of bronchiectasis management, as well as end-of-life costs.[56] We calculated age-specific, weighted-average costs of survival for each model cycle, and age-specific, weighted-average costs of death for each mortality event from general population estimates. This approach ensures a more comprehensive estimation of total healthcare expenditures over the modeled time horizon.

Productivity Costs

A meaningful difference in patients' productivity loss is expected to arise from the differential rate of exacerbations while we assumed that productivity losses for patients during non-exacerbated periods and for caregivers would be the same between Brensocatib and Usual Care. Pulmonary exacerbations can lead to increased absenteeism due to additional outpatient visits, sick leave, and hospitalizations in a subset of patients. The employee absence for exacerbation was estimated based on a review of the literature and expert opinion. For inclusion in the modified societal perspective analysis, productivity costs were calculated by multiplying the average market wage by the duration of absence. Key inputs for the indirect cost calculation are presented in Table E2.11.

Patients reported that daily airway clearance imposed a significant time burden on them and their caregivers. However, symptom scores did not materially differ between brensocatib- and placebo-treated patients in the ASPEN trial, relative to the threshold for clinical significance. [8,104] Therefore, we did not assume any effect of treatment on daily airway management.

Table E2.11: Inputs to Calculate Patient Productivity Costs

Inputs	Input Values	Sources
Absenteeism for Outpatient Visits for Each Exacerbation	5 days*	Tkacz, 2024[46] Expert opinion
Absenteeism for Inpatient Admission	10.8 days for a 14.7% of exacerbations	de la Rosa Carrillo, 2018 [105]
Sick Leave After a Hospital Admission	13 days for 7.1% of a hospital admission	de la Rosa Carrillo, 2018 [105]
Average Hourly Wage	$40.36†	IRS, 2025; U.S. Department of Labor, 2025 [106,107]

*Each exacerbation is assumed to require a minimum of two outpatient visits—one for initial diagnosis and another for follow-up monitoring. Each visit is estimated to take one entire working day for pre-procedure preparation, procedure for airway clearance and rehabilitation, diagnostic testing, pharmacy services, and travel time. To accounts for the recovery period while patients are recovered from the acute exacerbation, we tested the impact of a total of five days of absents from work (i.e., the number of business days for one week) in the scenario analysis.

†Loss of productivity for time seeking care, hourly: ($32.52 salary + $14.68 fringe benefit) × (1- 0.145 average income tax).

E3. Results

The undiscounted costs, life years, QALYs, evLYs, and exacerbations for brensocatib plus Usual Care and Usual Care alone are presented in Table E3.1. Discounted outcomes are available from the main report table 4.3.

Table E3.1. Undiscounted Results for Brensocatib + Usual Care vs Usual Care Alone

Treatment	Treatment Cost*	Cost, Other than Treatment	Total Costs†	QALYs	evLYs	Life Years	Number of Exacerbations
Brensocatib	$1,511,673	$438,551	$1,950,224	12.79	12.81	18.80	20.12
Usual Care	$28,258	$473,815	$502,074	12.58	12.58	18.70	24.27

evLYs: equal value of life years gained, QALY: quality-adjusted life year

*The cost of brensocatib was estimated using a placeholder price. Treatment costs include brensocatib and usual care cost. Life-time undiscounted costs of Brensocatib strategy includes $1,483,175 brensocatib costs and $28,498 usual care costs.

†Total costs include treatment (Brensocatib + Usual Care) and direct medical costs other than the treatment cost

E4. Sensitivity Analyses

One-Way Sensitivity Analysis

To demonstrate the effects of uncertainty on both costs and health outcomes, we varied each input values within a 95% confidence interval range. When 95% could not be calculated or approximated from available data, the range of each input for the one-way sensitivity analysis was varied ±25% of the base-case input. The incremental cost-effectiveness ratio was largely influenced by the relative risks of NTM infection, PsA infection, or exacerbation with brensocatib compared with placebo, the proportional utility weight for exacerbation, transition probabilities to PsA infection or NTM infection, rate of recovery from NTM infection, mortality ratio between PsA or NTM infection versus no infection, and utility of NCFB without exacerbation. Clinical inputs for the rate of transition between health states also had a moderate to large impact on ICER. All results remained above commonly accepted cost-effectiveness thresholds.

The Tornado Diagram is presented in Figure 4.2. The top 10 inputs having the greatest influence on the incremental cost-effectiveness ratios and results from the one-way sensitivity analysis can be found in Table E4.1.

Table E4.1. Tornado Diagram Inputs and Results for Brensocatib + Usual Care versus Usual Care Alone on incremental QALYs

	Lower Input*	Upper Input*	ICER† from Lower Input	ICER† from Upper Input
Relative Risk of the onset of NTM infection per cycle, brensocatib vs. placebo	0.46	1.33	$4,839,186	$58,340,984
Relative risk of the onset of PsA infection per cycle, brensocatib vs. placebo	0.46	1.33	$5,482,717	$18,908,621
Proportional utility weight for exacerbation	0.43	1	$5,452,670	$10,458,062
Relative risk of having exacerbation per cycle, brensocatib vs. placebo	0.69	0.94	$5,903,731	$10,470,107
Probability of transitioning to NTM, %	0.086	0.76	$10,036,011	$5,617,625
Probability of transitioning to PsA, %	0. 084	0. 50	$8,849,265	$6,245,911

Rate of recovery from NTM, % eradication or cure per cycle	3.03	8.16	$6,558,457	$8,522,266
Mortality rate ratio, NTM v. No NTM	1.03	2.11	$8,417,765	$6,579,902
Utility of NCFB without exacerbation	0.69	0.84	$7,807,250	$6,414,574
Mortality rate ratio, PsA v. No PsA	1.03	2.11	$8,128,397	$6,826,004

CE: cost-effectiveness, v: versus

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

†ICER: Incremental costs per quality adjusted life years gained for (Brensocatib + Usual Care) versus Usual Care.

Probabilistic Sensitivity Analysis

The incremental cost-effectiveness plane and acceptability curves for the probabilistic sensitivity analysis are presented in Figures E4.1. and E4.2.

Figure E4.1. Incremental Cost-Effectiveness Plane for Brensocatib + Usual Care versus Usual Care Alone

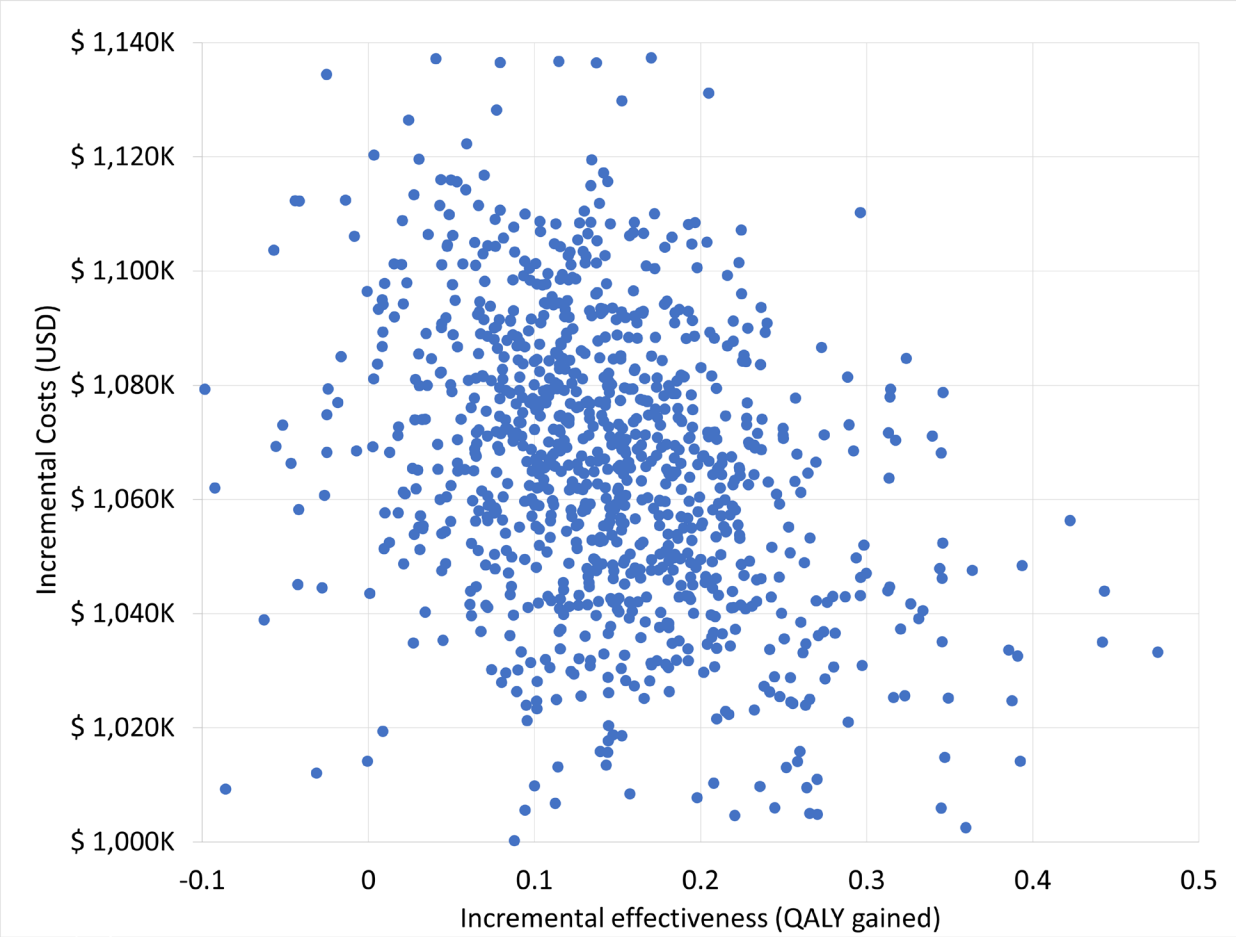


Figure E4.2. Acceptability Curve for Brensocatib + Usual Care versus Usual Care Alone

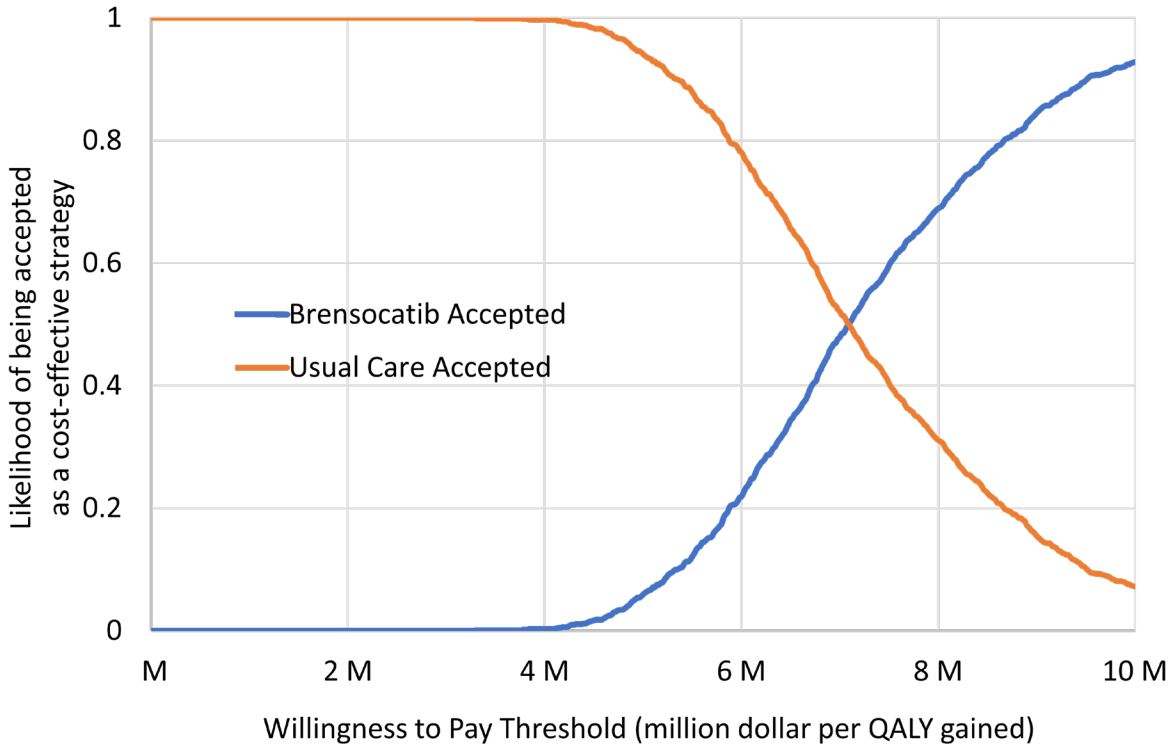


Table E4.2. Probabilistic Sensitivity Analysis Cost Per evLY Gained Results: Brensocatib + Usual Care versus Usual Care Alone

	Cost Effective at $50,000 per evLY Gained	Cost Effective at $100,000 per evLY Gained	Cost Effective at $150,000 per evLY Gained	Cost Effective at $200,000 per evLY Gained
Brensocatib + Usual Care	0%	0%	0%	0%

evLYs: equal value of life years gained

Table E4.3. Results of Probabilistic Sensitivity Analysis for Brensocatib + Usual Care versus Usual Care Alone

	Brensocatib, Mean	Usual Care, Mean	Incremental
Costs	$1,376,070	$ 310,660	$ 1,065,411
QALYs	9.69	9.54	0.14
evLYs	9.69	9.54	0.15
Incremental CE Ratio ($/QALY)			$ 7,440,560
Incremental CE Ratio ($/evLY)			$ 7,073,606
	Brensocatib, Median	**Usual Care, Median**	**Incremental**
Costs	$1,374,824	$ 306,334	$ 1,068,490
QALYs	9.65	9.51	0.14
evLYs	9.66	9.51	0.15
Incremental CE Ratio ($/QALY)			$ 7,371,746
Incremental CE Ratio ($/evLY)			$ 7,109,055

CE: cost-effectiveness, evLYs: equal-value life year, QALY: quality-adjusted life year

E5. Scenario Analyses

Table E5.1. Scenario Analysis Key Inputs

Inputs	Value	Source
Scenario 1: Modified Societal Perspective		
Absenteeism for Outpatient Visits for Each Exacerbation	5 days*	Tkacz, 2024; Expert opinion[46]
Absenteeism for Inpatient Admission	10.8 days for a 14.7% of exacerbations	de la Rosa Carrillo, 2018 [105]
Sick Leave After a Hospital Admission	13 days for 7.1% of a hospital admission	de la Rosa Carrillo, 2018 [105]
Average Hourly Wage	$40.36† ($323 daily)	U.S. Department of Labor, 2025[107]
Scenario 2: Decline in Lung Function Over the Lifetime		
FEV1 Decline Over the Lifetime	$FEV_{1\_male}=\exp[-9.37674+(0.00183\times Age)-(0.00011\times Age^2)+2.10839\times \ln(Height_{cm})]$ $FEV_{1\_female}=\exp[-8.49717+(0.00422\times Age)-(0.00015\times Age^2)+1.90019\times \ln(Height_{cm})]$ FEV1 trajectory reflect the estimates for male with 176 cm height and female with 162 cm height. For the model,	Falashetti, 2024; Einarson, 2015[60,62]

Inputs	Value	Source
	weighted average of male FEV1 and female FEV1 was used as input. FEV1 for NCFB patients will be 73% of the projected FEV1 for the target population. Impact of FEV_1 decline on utility was capped at 0.73 time of utility before adjusting for FEV_1 impact. The decision and assumption on the maximum decrease in the utility was based on the ratio of utility between severe and mild respiratory conditions abstracted from Einarson et al. Without this limitation, the utility loss associated with FEV_1 decline would exceed a reasonable range.	
Scenario 3: Difference in Lung Function Change Between Brensocatib and Placebo		
Decline in postbronchodilator FEV1 from baseline for brensocatib at 1 year	-24ml	Chalmers, 2025[8]
Decline in postbronchodilator FEV1 from baseline for placebo at 1 year	-62ml	Chalmers, 2025[8]
Scenario 4: Brensocatib 10mg		
Discontinuation rate	4.3%	Chalmers, 2025[8]
Risk Ratio for Exacerbation Brensocatib 10mg vs. Placebo	0.79	Chalmers, 2025[8]
Scenario 5: Subgroup analyses by chronic PsA infection		
PsA+ at baseline		
Incidence of Exacerbation (1 Month)‡ with usual care strategy	0.1458	Chalmers, 2025[8]
Risk Ratio for Exacerbation (Brensocatib vs. Placebo)	0.88	Chalmers, 2025[8]
PsA- at baseline		
Incidence of Exacerbation (1 Month)‡ with usual care strategy	0.0867	Chalmers, 2025[8]
Risk Ratio for Exacerbation (Brensocatib vs. Placebo)	0.77	Chalmers, 2025[8]
Scenario 6: Subgroup analyses by number of exacerbations		
2 exacerbations during 1 year baseline period		
Incidence of Exacerbation (1 Month)‡ with usual care strategy	0.0892	Chalmers, 2025[8]
Risk Ratio for Exacerbation	0.73	Chalmers, 2025[8]

Inputs	Value	Source
(Brensocatib vs. Placebo)		
3+ exacerbations during 1 year baseline period		
Incidence of Exacerbation (1 Month)‡ with usual care strategy	0.1517	Chalmers, 2025[8]
Risk Ratio for Exacerbation (Brensocatib vs. Placebo)	0.85	Chalmers, 2025[8]

FEV1: Forced Expiratory Volume in 1 second; PsA: Pseudomonas Aeruginosa

*Each exacerbation is assumed to require a minimum of two outpatient visits—one for initial diagnosis and another for follow-up monitoring. Each visit is estimated to take one entire working day for pre-procedure preparation, procedure for airway clearance and rehabilitation, diagnostic testing, pharmacy services, and travel time.

†Loss of productivity for time seeking care, hourly: ($32.52 salary + $14.68 fringe benefit) × (1- 0.145 average income tax).

‡Monthly incidence of exacerbation was calculated from yearly rate of exacerbation. Rate of exacerbation in each subgroup was calculated from the ASPEN clinical trial data using simultaneous linear equations.

Scenario Analysis 1: Modified Societal Perspective

Modified societal perspective included productivity losses from absenteeism attributed to bronchiectasis pulmonary exacerbations. Exacerbations can lead to absenteeism due to additional outpatient visits, sick leave, and hospitalizations in a subset of patients. Results are presented in Table E5.2.

Table E5.2. Discounted Results for Modified Societal Perspective

Treatment	Direct Costs*	Indirect Costs†	Total Costs	QALYs	evLYs	Life Years
Brensocatib + Usual Care	$1,417,963	$11,704	$1,429,667	9.32	9.33	13.72
Usual Care	$361,301	$14,131	$375,433	9.18	9.18	13.67

evLYs: equal value of life years gained, QALY: quality-adjusted life year

*The cost of brensocatib was estimated using a placeholder price. Direct costs include treatment, usual care, outpatient, and admission costs.

†Indirect costs include productivity losses from absenteeism due to additional outpatient visits, sick leave, and hospitalizations.

Scenario Analysis 2: Decline in Lung Function

In Scenario 2, the changes in quality of life associated with the decrease in FEV1 were applied to the model. Results are presented in Table E5.3. The calculated Incremental cost effectiveness ratios were $8,444,540 per QALY gained and $7,343,113 per evLY gained.

Table E5.3. Discounted Results for Decline in Lung Function

Treatment	Treatment Cost*	Cost, Other Than Treatment	Total Costs†	QALYs	evLYs	Life Years	Total Number of Exacerbations‡
Brensocatib + Usual Care	$1,103,211	$314,753	$1,417,963	7.61	7.63	13.72	14.69
Usual Care	$20,649	$340,652	$361,301	7.48	7.48	13.67	17.73

evLYs: equal value of life years gained, QALY: quality-adjusted life year

*The cost of brensocatib was estimated using a placeholder price. Treatment costs include brensocatib (if brensocatib strategy) and usual care cost.

†Total costs include treatment (Brensocatib + usual care) and direct medical costs other than the treatment cost

‡Total number of exacerbations was discounted at an annual rate of 3%.

Scenario Analysis 3: Difference in Lung Function Change Between Brensocatib and Placebo

In Scenario 3, the differential rate of decline in FEV1 between brensocatib and placebo was applied.[8] Results are presented in Table E5.4. The scenario 2 resulted in an incremental cost-effectiveness ratios of $2,195,677 per QALY gained and $2,151,460 per evLY gained.

Table E5.4. Discounted Results for Difference in Lung Function Change between Brensocatib and Placebo

Treatment	Treatment Cost*	Cost, Other Than Treatment	Total Costs†	QALYs	evLYs	Life Years	Total Number of Exacerbations‡
Brensocatib + Usual Care	$1,103,211	$314,753	$1,417,963	9.13	9.14	13.72	14.69
Usual Care	$20,649	$340,652	$361,301	8.65	8.65	13.67	17.73

evLYs: equal value of life years gained, QALY: quality-adjusted life year

*The cost of brensocatib was estimated using a placeholder price. Treatment costs include brensocatib (if brensocatib strategy) and usual care cost.

†Total costs include treatment (Brensocatib + usual care) and direct medical costs other than the treatment cost

‡Total number of exacerbations was discounted at an annual rate of 3%.

Scenario Analysis 4: Brensocatib 10 mg

Scenario analysis 4 replaced the rate of exacerbation input derived from 25mg outcome with the input derived from brensocatib 10mg outcome. Results are presented in Table E5.5. The scenario 4 resulted in an incremental cost-effectiveness ratios of $7,373,269 per QALY gained and $6,928,809 per evLY gained.

Table E5.5. Discounted Results for Brensocatib 10mg

Treatment	Treatment Cost*	Cost, Other Than Treatment	Total Costs†	QALYs	evLYs	Life Years	Total Number of Exacerbations‡
Brensocatib + Usual Care	$1,097,627	$312,848	$1,410,475	9.32	9.33	13.72	14.28
Usual Care	$20,650	$340,097	$360,747	9.18	9.18	13.67	17.61

evLYs: equal value of life years gained, QALY: quality-adjusted life year

*The cost of brensocatib was estimated using a placeholder price. Treatment costs include brensocatib (if brensocatib strategy) and usual care cost.

†Total costs include treatment (Brensocatib + usual care) and direct medical costs other than the treatment cost

‡Total number of exacerbations was discounted at an annual rate of 3%.

Scenario Analysis 5 & 6: Subgroup Analyses by Baseline Characteristics

Subgroup analyses by presence of chronic PsA infection at baseline, and number of exacerbations in the 12 months prior to starting treatment were conducted in scenario 5 and 6. Results are presented in Table E5.6A and 5.6B, respectively.

Table E5.6A. Discounted Results by Presence of Chronic PsA Infection at Baseline

Treatment	Treatment Cost*	Cost, Other Than Treatment	Total Costs†	QALYs	evLYs	Life Years	Total Number of Exacerbations‡
PsA Infection Positive							
Brensocatib + Usual Care	$1,093,683	$373,508	$1,467,191	8.96	8.97	13.60	20.65
Usual Care	$20,476	$395,544	$416,020	8.84	8.84	13.55	23.00
PsA Infection Negative							
Brensocatib + Usual Care	$1,108,344	$282,894	$1,391,238	9.51	9.52	13.79	11.43
Usual Care	$20,745	$309,252	$329,997	9.37	9.37	13.73	14.50

evLYs: equal value of life years gained, QALY: quality-adjusted life year

*The cost of brensocatib was estimated using a placeholder price. Treatment costs include brensocatib (if brensocatib strategy) and usual care cost.

†Total costs include treatment (Brensocatib + usual care) and direct medical costs other than the treatment cost

‡Total number of exacerbations was discounted at an annual rate of 3%.

Table E5.6B. Discounted Results by Number of Exacerbations in the 12 Months Prior to Treatment

Treatment	Treatment Cost*	Cost, Other Than Treatment	Total Costs†	QALYs	evLYs	Life Years	Total Number of Exacerbations‡
2 Exacerbations							
Brensocatib + Usual Care	$1,104,421	$298,371	$1,402,792	9.38	9.39	13.74	11.18
Usual Care	$20,668	$327,403	$348,071	9.23	9.23	13.68	14.89
3 or More Exacerbations							
Brensocatib + Usual Care	$1,101,169	$342,874	$1,444,042	9.21	9.22	13.70	20.70
Usual Care	$20,611	$368,774	$389,385	9.07	9.07	13.64	23.75

evLYs: equal value of life years gained, QALY: quality-adjusted life year

*The cost of brensocatib was estimated using a placeholder price. Treatment costs include brensocatib (if brensocatib strategy) and usual care cost.

†Total costs include treatment (Brensocatib + usual care) and direct medical costs other than the treatment cost

‡Total number of exacerbations was discounted at an annual rate of 3%.

Scenario Analysis 7: Accelerating Exacerbation Rate

We applied a time-varying exacerbation rate, which allows for an accelerating risk of exacerbation over the lifetime. In each year, the rate of exacerbation was accelerated by 2.5% and 5% of the exacerbation rate of the previous year. With the 2.5% annual increase in risk, the incremental cost-effectiveness ratios were $6,923,523 per QALY gained and $6,484,747 per evLY gained. For a 5% annual increase, the incremental cost-effectiveness ratios were $6,388,708 per QALY gained and $5,962,678 per evLY gained (Table E5.7).

Table E5.7. Discounted Results by Presence of Chronic PsA Infection at Baseline

Treatment	Treatment Cost*	Cost, Other Than Treatment	Total Costs†	QALYs	evLYs	Life Years	Total Number of Exacerbations‡
0% annual increase in the risk of exacerbation							
Brensocatib + Usual Care	$1,103,211	$314,753	$1,417,963	9.32	9.33	13.72	14.68
Usual Care	$20,649	$340,652	$361,301	9.18	9.18	13.67	17.73
2.5% annual increase in the risk of exacerbation							
Brensocatib + Usual Care	$1,101,593	$332,133	$1,433,726	9.25	9.26	13.70	18.42
Usual Care	$20,614	$360,874	$381,488	9.09	9.09	13.64	22.09
5% annual increase in the risk of exacerbation							
Brensocatib + Usual Care	$1,099,451	$354,443	$1,453,894	9.15	9.16	13.68	23.23
Usual Care	$20,568	$386,194	$406,763	8.99	8.99	13.61	27.54

evLYs: equal value of life years gained, QALY: quality-adjusted life year
*The cost of brensocatib was estimated using a placeholder price. Treatment costs include brensocatib (if brensocatib strategy) and usual care cost.
†Total costs include treatment (Brensocatib + usual care) and direct medical costs other than the treatment cost
‡Total number of exacerbations was discounted at an annual rate of 3%.

E6. Heterogeneity and Subgroups

Subgroup analyses were conducted as scenario analyses to examine the effect of treatment selection on the rate of exacerbation stratified by presence of chronic PsA infection at baseline and the number of exacerbations in prior 12 months. Inputs are reported in Table E2.7 and E2.8, and the results are presented in Table E5.6A and E5.6B.

Model Validation

We used several approaches to validate the model. First, we provided preliminary model structure, methods and assumptions to manufacturers and patient groups. Based on feedback from these groups, we refined data inputs used in the model, as needed. Second, we varied model input parameters to evaluate face validity of changes in results. Additionally, we performed model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we shared the model for external verification around the time of publishing the draft report. Finally, we compared results to other cost-effectiveness models in this therapy area.

The outputs from the model were validated against the trial data for the intervention and also any relevant observational datasets. The total number of exacerbations from our model for the first-year of the treatment was 1.07 and 1.30 for Brensocatib + usual care and Usual Care alone, respectively. The projected numbers of exacerbation were similar to the annualized rate from the clinical trial (1.04 [0.93 to 1.16] for brensocatib 25mg and 1.29 [1.16 to 1.43] and within the 95% confidence intervals.[8] Nominal differences between the model outputs and clinical trials on the annual rate of exacerbation may be attributable to the rate of chronic infection and recovery that we identified from a literature review, due to the lack of input value from the clinical trial. In a follow-up analysis we tested the influence of replacing the exacerbation rate inputs with 0.091 for Brensocatib and 0.107 for Usual Care, respectively, calculating the number of exacerbations over the first year matched with the clinical trial data. This input value replacement did not alter the ICER nor changed conclusion. In summary our model results closely matched findings from the clinical trial.

We also compared the simulated mortality with the anticipated life expectancy among patients with chronic pulmonary conditions. According to the 2025 Trustees Report and US Social Security, the remaining life expectancy of 60 year-old males and females is 21.08 and 24.12 years, respectively,[63] which calculate the weighted average of 23 years. Our modeling approach produced the undiscounted life-expectancy of 18.8 years for Brensocatib and 18.7 years for the Usual Care strategy, which is 4.2 to 4.3 years shorter than the general-population life expectancy. Considering that individuals with Stage 2 COPD (moderate COPD with FEV1 50%-79%) and stage 3 COPD (emphysema/chronic bronchitis) have been found to have a 2.2 to 5.8 year reduction in life-expectancy compared to the general population, the modeled life-expectancy for patients in our model appears reasonable.[64,65]

Prior Economic Models

When it comes to evaluating the long-term costs and effectiveness of interventions to treat patients with NCFB, our study represents a first attempt. Therefore, it cannot be directly compared with existing economic models. Through a systematic literature review, we identified previous studies analyzing cost or effectiveness of interventions aimed at alleviating bronchiectasis symptoms among immunocompromised or general respiratory conditions, which are outlined and compared in this section.

According to an abstract published in 2014, Bhattacharyya at al. developed a *de-novo* economic model to assess consequences of NCFB.[35] Using four health states defined by various level of exacerbations, the author estimated that a 35% reduction of exacerbation rates reduced the 3.23 hospitalizations per patient over a life time and reduced 1 death per 600 patients over a 10 year period. Due to the limited information available from the published abstract and the absence of full

model structure, detailed methods and inputs for this study cannot be compared with our approach.

Milne at al., analyzed the cost-effectiveness of one-year air humidification therapy for patients with chronic respiratory conditions, including COPD and bronchiectasis.[36] Rather than employing a model-based approach, the study utilized the clinical trial data, hospital records and patient diary to estimate the direct healthcare costs, SGRQ and QALY changes associated with a continuous humidification therapy for a 12-month follow up in New Zealand healthcare setting. Although the therapy shows potential for long-term use in patients with chronic respiratory conditions, the study focused on a timeframe limited to the duration of the clinical trial. For this reason, the study method is not suitable to be applied for the projection of long-term benefits. Furthermore, the input values were not specifically identified for the patients with bronchiectasis, the generalizability of the study findings our target population with the confirmed diagnosis with non-cystic fibrosis bronchiectasis is limited.

Windegger at al., developed a *de novo* Markov model and projected the costs and utility of immunoglobulin treatment for patients with immunodeficiency disease for which bronchiectasis was the major concern.[38] The study elucidated the impact of pseudomonas aeruginosa infection in patients with bronchiectasis, and such structural advance is well aligned with the experts' concern on the progression of bronchiectasis. While we adopted a similar model structure, including chronic infection, input values utilized in the study were not appropriate for our target population of patients with NCFB and two or more exacerbations in the previous year. Further, the clinical and costs data were collected from a small cohort (n=14) of patients with primary immunodeficiency disease, including both bronchiectasis and non-bronchiectasis patients. Therefore, this study provided limited usefulness as a source of inputs or for comparison with our results.

van Wilder et al., included severity of infection into a model.[37] The investigator group analyzed healthcare costs, life expectancy and quality of life of immunoglobulin replacement therapy (IgGRT) in patients with common variable immunodeficiency disorders (CVID). Although bronchiectasis-related conditions such as infection and chronic lung disorder were the major health states in the model, the target population of van Wilder at al. is much heterogeneous and included patients with autoimmune disorders living with risks of developing chronic lung disorders. Thus the structure, inputs and results are not applicable for the patients eligible to receive brensocatib.

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons.

The potential budget impact analysis included the candidate populations eligible for treatment: patients with NCFB. To estimate the size of the potential candidate populations for treatment, we used inputs bronchiectasis prevalence by age group in the US and applied these estimates to the corresponding size of the US population by age group averaged over the next five years.[6,66] This resulted in an overall prevalence rate of 0.156% and a total eligible population estimate of 461,208 patients in the US. For the purposes of this analysis, we assumed that 20% of these patients would initiate treatment in each of the five years, or 92,242 patients per year.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[108,109] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Once estimates of budget impact are calculated, we compare our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (Value Assessment Framework), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2024-2025, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $880 million per year for new drugs.