Brensocatib for Non-Cystic Fibrosis Bronchiectasis

Draft Background and Scope

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Background

Bronchiectasis is a chronic lung disease that affects breathing and coughing. Although patients have different symptoms, many have chronic cough, often bringing up mucus and saliva, and exacerbations that may involve worsening of these chronic symptoms along with shortness of breath.[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] The coughing and mucus production make bronchiectasis similar to chronic obstructive pulmonary syndrome (COPD). However, unlike COPD, bronchiectasis is a disorder of the bronchi enlarging rather than collapsing.[4] 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 is common among individuals with cystic fibrosis. 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]

In the United States, NCFB is relatively common and increasingly recognized. NCFB is substantially more common than cystic fibrosis. An estimated 350,000 to 500,000 adults in the United States have NCFB, with 70,000 new cases emerging annually.[6] Older estimates previously suggested lower prevalence.[7,8] The increasing measured prevalence may reflect an actual increase in prevalence of NCFB and/or increased detection, particularly with higher use of high-resolution CT scans. The annual cost of NCFB care in the United States exceeds $14 billion per year, about $2 billion of which is for hospitalizations. Other important contributions to cost include labs, 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.[9]

Among those with NCFB, about two-thirds have at least one exacerbation 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.[10] Risk markers for bronchiectasis include prior hospitalizations and exacerbations, severity of shortness of breath, lower forced expiratory volume in one second (amount of air the lung can force out in one second), colonization with bacteria (including the very resistant *Pseudomonas aeruginosa*), the number of parts of the lung involved, age, and body-mass index.[11]

Clinical guidelines for NCFB are based on generally low-quality evidence and interventions are directed at different components of the "vicious cycle." 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 and oral antibiotics are recommended. Pulmonary rehabilitation is recommended for individuals who are substantially limited by shortness of breath. In rare, severe cases, surgical resection of part of the lung or even lung transplantation is sometimes considered.[12] 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 a key driver of the "vicious cycle." 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.[13]

Stakeholder Input

This draft scoping document was developed through outreach and engagement of diverse stakeholders, including patients and their families, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. A revised scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Discussions with clinical experts emphasized the substantial burden that patients with NCFB face, often coughing with mucus production every day and spending 30-60 minutes daily with home respiratory therapy and nebulizers. There is hope that a new agent could reduce this amount of time in home self-care and potentially help individuals feel better later in the day. There is a lot of interest in brensocatib, since no FDA approved treatment exists and there have been a lot of therapeutic failures for NCFB (including the recognition that many cystic fibrosis treatments do not work well for NCFB).

Clinical experts also shared that they expect brensocatib to be used for outpatients with NCFB, potentially indefinitely. They believe that matching treatment to those most likely to benefit would be important, potentially aided with risk markers. How brensocatib affects utilization will be important. One clinical expert perceived different thresholds for hospital admission during exacerbations. For example, at highly specialized centers, the proportion of exacerbations that result in hospitalization may be lower than at other centers. Often outpatient visits occur every three to six months, more frequently if not well controlled. The diagnosis of NCFB is clinical with supporting radiographic evidence, and there is no specific test. The apparent increase in prevalence is likely related to increased awareness and high-resolution imaging.

Academic reports based on patient perspectives suggest that patients and caregivers are concerned about symptoms including persistent cough, shortness of breath, and mucus production. Misdiagnosis and delayed diagnosis are common, and associated with additional emotional burdens of anger, confusion, frustration, and anxiety.[14] Patients report that their quality of life is affected by social embarrassment, sleep disturbance, anxiety, and the need to modify daily and future activities.[15] Patients also report difficulty finding physicians 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.[16]

Report Aim

This project will evaluate the health and economic outcomes of brensocatib for NCFB. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

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

Data permitting, we will 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)
- Bronchiectasis Severity Index Score

Interventions

The intervention of interest of this review is:

- Brensocatib (Insmed Pharmaceuticals)

Comparators

Data permitting, we intend to compare brensocatib as an add-on therapy to current usual care, which may include antibiotics, mucolytics, pulmonary rehabilitation, and airway clearance devices, 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 Outcome
    - 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 will be derived from studies of any duration.

Settings

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

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 would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities*
There is substantial unmet need despite currently available treatments.
This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the healthcare system.
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 treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.

*Benefits beyond health and special ethical priorities shape to some extent how the value of any effective treatments for a particular condition will be judged and are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society. For additional information, please see the ICER Value Assessment Framework.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

A detailed economic model analysis plan with proposed methodology, model structure, model parameters, model inputs, and model assumptions will be published on June 6, 2025. This scoping document provides early thoughts about the overall model structure.

As a complement to the evidence review, we will develop a *de-novo* economic model to assess the lifetime cost-effectiveness of brensocatib as an add-on therapy to usual care, which may include antibiotics, mucolytics, pulmonary rehabilitation, and airway clearance devices, compared with usual care alone. The model structure will be developed based in part on models identified through a targeted systematic literature review of economic analyses of treatments for bronchiectasis.[17-20]

Analyses will be conducted from the health care system perspective including direct medical care costs only. Patient and caregiver productivity, and other indirect costs will be considered in a modified societal perspective analysis. The modified societal perspective will be considered as a co-base case when (a) direct data on indirect costs are available, (b) the societal costs of care are large relative to direct health care costs, and (c) the impact of treatment on the indirect costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. If direct data are lacking on patient and/or caregiver productivity, we will implement a method to capture the potential impacts of brensocatib on productivity (patient and caregiver).

The target population will consist of adolescents and adults with NCFB. The analytic cohort consists of patients who previously had at least two exacerbations in the previous year. The model will consist of four health states that are: patients with NCFB 1) without exacerbation, 2) with exacerbation, 3) with chronic *Pseudomonas aeruginosa* infection, and 4) who have died. Provided that a significant proportion of exacerbation requires hospital admission and short-term extensive care, a stand-alone inpatient admission state may be added to the model as a transient state. A cohort of patients will be modeled as they transition between states during predetermined cycles (i.e., monthly) over a lifetime time horizon, modeling patients from treatment initiation until death. Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between the intervention and usual care. Treatment effectiveness will be estimated using data from clinical trials for both the treatment and comparator.[21,22] We will also consider expert opinion as the source of model inputs when insufficient evidence exists identifying those inputs from published literature.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of pulmonary exacerbations avoided, life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained (evLYG). Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, patient and caregiver productivity changes and other indirect costs will be included in a separate analysis, as available data allow. In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

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 additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by brensocatib (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. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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