ORIGINAL ARTICLE

# Phase 2 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis

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## ABSTRACT

### BACKGROUND

Patients with bronchiectasis have frequent exacerbations that are thought to be related to neutrophilic inflammation. The activity and quantity of neutrophil serine proteases, including neutrophil elastase, are increased in the sputum of patients with bronchiectasis at baseline and increase further during exacerbations. Brensocatib (INS1007) is an oral reversible inhibitor of dipeptidyl peptidase 1 (DPP-1), an enzyme responsible for the activation of neutrophil serine proteases.

### METHODS

In a phase 2, randomized, double-blind, placebo-controlled trial, we randomly assigned, in a 1:1:1 ratio, patients with bronchiectasis who had had at least two exacerbations in the previous year to receive placebo, 10 mg of brensocatib, or 25 mg of brensocatib once daily for 24 weeks. The time to the first exacerbation (primary end point), the rate of exacerbations (secondary end point), sputum neutrophil elastase activity, and safety were assessed.

### RESULTS

Of 256 patients, 87 were assigned to receive placebo, 82 to receive 10 mg of brensocatib, and 87 to receive 25 mg of brensocatib. The 25th percentile of the time to the first exacerbation was 67 days in the placebo group, 134 days in the 10-mg brensocatib group, and 96 days in the 25-mg brensocatib group. Brensocatib treatment prolonged the time to the first exacerbation as compared with placebo (P=0.03 for 10-mg brensocatib vs. placebo; P=0.04 for 25-mg brensocatib vs. placebo). The adjusted hazard ratio for exacerbation in the comparison of brensocatib with placebo was 0.58 (95% confidence interval [CI], 0.35 to 0.95) in the 10-mg group (P=0.03) and 0.62 (95% CI, 0.38 to 0.99) in the 25-mg group (P=0.046). The incidence-rate ratio was 0.64 (95% CI, 0.42 to 0.98) in the 10-mg group, as compared with placebo (P=0.04), and 0.75 (95% CI, 0.50 to 1.13) in the 25-mg group, as compared with placebo (P=0.17). With both brensocatib doses, sputum neutrophil elastase activity was reduced from baseline over the 24-week treatment period. The incidence of dental and skin adverse events of special interest was higher with the 10-mg and 25-mg brensocatib doses, respectively, than with placebo.

### CONCLUSIONS

In this 24-week trial, reduction of neutrophil serine protease activity with brensocatib in patients with bronchiectasis was associated with improvements in bronchiectasis clinical outcomes. (Funded by Insmed; WILLOW ClinicalTrials.gov number, NCT03218917.)

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Non–cystic fibrosis bronchiectasis (referred to here as bronchiectasis) is a chronic inflammatory disease defined as permanent dilatation of the bronchi.[1] Patients characteristically have a daily cough and sputum production, as well as frequent exacerbations. Exacerbations are independently associated with a poor quality of life, decreased lung function, and increased mortality.[1-3]

Inflammation in bronchiectasis is dominated by neutrophils that, when activated, release neutrophil serine proteases, including neutrophil elastase, which is believed to be central to the pathophysiology of bronchiectasis.[4,5] It is thought that elevated levels of neutrophil elastase, proteinase 3, and cathepsin G overwhelm natural inhibitors, such as alpha$_1$-antitrypsin and secretory leukocyte protease inhibitor,[6,7] which alters the microenvironment and increases the risk of infection.[8,9]

Neutrophil serine proteases are activated during neutrophil maturation in the bone marrow by dipeptidyl peptidase 1 (DPP-1; also known as cathepsin C) by removing the N-terminal dipeptide; this allows active enzymes to be packaged into granules before the release of neutrophils into the circulation.[10] Brensocatib (INS1007) is an oral, selective, competitive, and reversible inhibitor of DPP-1 that has been shown to inhibit neutrophil serine protease activity in the blood of healthy volunteers.[10] To examine whether brensocatib reduces the incidence of exacerbations of bronchiectasis, we conducted a phase 2, randomized, placebo-controlled, dose-ranging trial (WILLOW).

## Methods

### Trial Design and Patients

We conducted this double-blind, parallel-group trial at 116 sites across 14 countries (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Eligible patients were 18 to 85 years of age and had a clinical history consistent with bronchiectasis (cough, chronic sputum production, or recurrent respiratory infections), as confirmed on computed tomography of the chest. Patients had to have at least two documented exacerbations in the previous 12 months, a history of chronic sputum expectoration, sputum color at screening that was rated as being mucopurulent or purulent according to a validated color chart,[11] and the ability to provide a sputum sample during screening.

Key exclusion criteria were bronchiectasis due to a clinical diagnosis of cystic fibrosis, hypogammaglobulinemia, common variable immunodeficiency, or alpha$_1$-antitrypsin deficiency, as well as an investigator-determined primary diagnosis of chronic obstructive pulmonary disease or asthma (secondary diagnoses were allowed). Because of potential dental side effects of treatment with brensocatib, exclusion criteria were structured to avoid the enrollment of patients with severe periodontitis. Complete eligibility criteria are provided in the Supplementary Appendix.

### Trial Oversight

The sponsor, Insmed, developed the protocol with the lead investigator (first author) and conducted the data analyses. The initial draft of the manuscript was written by the first author. Subsequent drafts were revised and edited by all the authors with the assistance of a medical writer, funded by Insmed in accordance with the third edition of the Good Publication Practice guidelines. All the authors made the decision to submit the manuscript for publication. All the authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the final protocol, available at NEJM.org.

The trial was performed in accordance with the ethical principles of the Declaration of Helsinki,[12] the Good Clinical Practice guidelines of the International Council for Harmonisation,[13] and applicable regulatory requirements. Approvals from independent ethics committees were obtained. All the patients provided written informed consent. An independent, external data and safety monitoring committee (comprising physicians with pulmonary expertise, a statistician experienced in the evaluation of clinical safety, and experts in periodontal disease and dermatology) reviewed all adverse events.

### Trial Procedures

Patients who completed the 6-week screening period (which included up to two dental visits to establish baseline periodontal health) and met the eligibility criteria were randomly assigned in a 1:1:1 ratio by means of a central interactive

Web-response system to receive an oral dose of placebo, 10 mg of brensocatib, or 25 mg of brensocatib once daily. Clinic visits occurred on day 1 (baseline), during weeks 2, 4, 8, 12, 16, 20, and 24 (the end of the treatment period), and at week 28 (4 weeks after the end of the treatment period) (Fig. S1). Randomization was stratified according to long-term macrolide use (≥6 months of treatment before screening visit; yes vs. no) and *Pseudomonas aeruginosa* infection (positive sputum sample at screening; yes vs. no). Treatment adherence was defined as taking 80 to 125% of the intended quantity of brensocatib or placebo and was monitored by means of tablet counts. A sputum sample was obtained during clinic visits; if a patient was unable to provide a spontaneous sputum sample during any post-baseline visit, chest physiotherapy was performed to facilitate expectoration. If chest physiotherapy did not result in a sputum sample, sputum induction was performed (see the Supplementary Appendix). Neutrophil elastase was measured in sputum in the pharmacodynamic population by an activity-based immunoassay (ProteaseTag, ProAxsis). The pharmacodynamic population included all the patients who received at least one dose of brensocatib or placebo and underwent at least one measurement of neutrophil elastase before and after receipt of the dose.

Exacerbations were defined according to modified consensus criteria[14] as the presence of at least three of the following symptoms for at least 48 hours that resulted in a physician's decision to prescribe an antibiotic agent: increased cough, increased sputum volume or change in sputum consistency, increased sputum purulence, increased breathlessness or decreased exercise tolerance, fatigue or malaise, and hemoptysis. Severe exacerbations were those that led to hospitalization.[14]

Assessments of efficacy were conducted and the Quality of Life–Bronchiectasis questionnaire (range, 0 to 100, with higher scores indicating a better quality of life; minimum clinically important difference [MCID], 8 points) and the Leicester Cough Questionnaire (range, 0 to 21, with higher scores indicating a better quality of life; MCID, 1.3 points) were administered throughout the 24-week treatment period (8 visits). The score on the St. George's Respiratory Questionnaire (range, 0 to 100, with higher scores indicating greater impairment; MCID, 4 points) was evaluated at baseline, at week 12, and at week 24 (end of treatment period).

Safety end points that were monitored from enrollment through week 28 (4 weeks after the end of the treatment period) included adverse events, 12-lead electrocardiographic measurements, clinical laboratory testing results, vital signs, physical examination results, and pulmonary-function tests as assessed by spirometry after bronchodilator use (forced expiratory volume in 1 second [$FEV_1$], forced vital capacity [FVC], peak expiratory flow rate, and forced expiratory flow between 25% and 75% of the FVC). During each visit, investigators were responsible for the detection and documentation of adverse events by means of general queries and examination of the oral soft tissues and skin.

Periodontal disease and skin hyperkeratosis were adverse events of special interest that were informed by clinical presentation of Papillon–Lefèvre syndrome, a rare autosomal recessive disorder caused by the genetic absence of DPP-1, which manifests with diffuse palmoplantar keratoderma and periodontitis leading to premature deciduous tooth loss and permanent dentition at a young age.[15] All the patients, excluding those who were edentulous, underwent dental assessment at baseline and at weeks 8 and 24. Severe infections were also monitored as adverse events of special interest. Additional details are provided in the Adverse Events of Special Interest section in the Supplementary Appendix.

### END POINTS AND ASSESSMENTS

The primary efficacy end point was the time to the first exacerbation during the 24-week treatment period. Secondary efficacy end points were the rate of exacerbations (number of events per patient-year), the change from screening in the percent of the predicted $FEV_1$ after bronchodilator use, the change from baseline in the Respiratory Symptoms score on the Quality of Life–Bronchiectasis questionnaire, and the change in the concentration of active neutrophil elastase in sputum from baseline (mean of the concentrations at screening and day 1) to the value during the treatment period (mean of the concentrations at weeks 12 and 24). Subgroup analyses of the time to exacerbation and the rate of exacerbation were planned exploratory end points. Changes

in other domains on the Quality of Life–Bronchiectasis questionnaire, in the score on the St. George's Respiratory Questionnaire, and in the score on the Leicester Cough Questionnaire were prespecified exploratory measures.

### STATISTICAL ANALYSIS

The sample size was estimated on the basis of a predicted exacerbation rate in the placebo group of 1.2 events per patient per year.[16] Thus, it was estimated that the random assignment of 216 patients, in a 1:1:1 ratio across the three trial groups, with 72 patients per group completing the trial, would provide the trial with 80% power to detect a hazard ratio of 0.58 (e.g., an approximate 40% difference in the time to the first exacerbation). We aimed to enroll 240 patients to ensure that approximately 216 patients would complete the trial.

Efficacy analyses were based on the intention-to-treat population, which comprised all the patients who had undergone randomization. The primary efficacy end point, the time to the first exacerbation, was analyzed with the use of Kaplan–Meier survival analyses, with comparisons between the trial groups made by means of the stratified log-rank test. In a sensitivity analysis, patients who discontinued the trial prematurely were counted as having a failure event (exacerbation event) rather than as having a censoring event in the time-to-event analysis. We used Cox proportional-hazards analysis as a sensitivity analysis to determine adjusted hazard ratios for the time to the first exacerbation. The secondary end point of the rate of exacerbations was analyzed by a Cochran–Mantel–Haenszel test (percentage of patients who had an exacerbation). We used two prespecified sensitivity analyses to assess the annualized event rate and the relative risk (negative binomial model) and the time to recurrent events (Anderson–Gill model). For subgroup analyses, unadjusted hazard ratio estimates were obtained from the Cox proportional-hazards model. The difference in the incidence of adverse events between each brensocatib group and the placebo group was analyzed by a chi-square test. More information about the secondary end points is provided in the Statistical Analyses and Data Collection section in the Supplementary Appendix.

Analyses are presented with two-sided P values, with the level of significance set at 0.05. The methods of analysis that we used account for loss to follow-up, and there was no imputation of missing data. To address multiplicity across end points, secondary end points were assessed hierarchically in the following order: the rate of exacerbations, the change in the percent of the predicted $FEV_1$, the change in the Respiratory Symptoms domain score on the Quality of Life–Bronchiectasis questionnaire, and change in sputum neutrophil elastase activity. Once an end point did not reach significance at either brensocatib dose, no further significance would be inferred for the end points lower down the statistical hierarchy. Additional details of the statistical analysis are provided in the Supplementary Appendix.

## RESULTS

### PATIENT POPULATION

Overall, 416 patients underwent screening and 256 underwent randomization. A total of 87 patients were assigned to the placebo group, 82 to the 10-mg brensocatib group, and 87 to the 25-mg brensocatib group; 85% of the patients in the placebo group, 93% of those in the 10-mg brensocatib group, and 86% of those in the 25-mg brensocatib group completed the trial (Fig. S2 and Table S1). Adherence to the trial regimen was 90%, 93%, and 90%, respectively.

The demographic and clinical characteristics of the patients at baseline were similar across the trial groups (Table 1 and Table S2). Patients were predominately White, female, and older than 60 years of age. The baseline concentration of neutrophil elastase in sputum was below the lower limit of quantification in 21% of the patients in the placebo group, in 28% of those in the 10-mg brensocatib group, and in 24% of those in the 25-mg brensocatib group.

### PRIMARY END POINT

The median time to the first exacerbation was 189 days in the placebo group, but because of the low number of exacerbations in the two brensocatib groups, the median time to the first exacerbation could not be estimated in those groups. The 25th percentile of the time to the first exacerbation was 67 days in the placebo group, 134 days in the 10-mg brensocatib group, and 96 days in the 25-mg brensocatib group. The time to the first exacerbation was significantly

**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).***

| Characteristic | Placebo (N=87) | 10-mg Brensocatib (N=82) | 25-mg Brensocatib (N=87) |
|---|---|---|---|
| Age — yr | 64.0±11.9 | 64.6±12.4 | 63.7±12.7 |
| Female sex — no. (%) | 55 (63) | 57 (70) | 62 (71) |
| White race — no. (%)† | 71 (82) | 76 (93) | 78 (90) |
| Long-term macrolide use — no. (%)‡ | 14 (16) | 10 (12) | 16 (18) |
| Use of inhaled glucocorticoids — no. (%) | 52 (60) | 43 (52) | 49 (56) |
| *Pseudomonas aeruginosa*–positive — no. (%)‡§ | 29 (33) | 27 (33) | 33 (38) |
| Median Bronchiectasis Severity Index score (range)¶ | 7 (0–19) | 8 (1–21) | 8 (0–19) |
| ≥3 Exacerbations in previous 12 mo — no. (%) | 25 (29) | 23 (28) | 36 (41) |
| Hospitalized for exacerbation in previous 24 mo — no. (%) | 30 (34) | 31 (38) | 31 (36) |
| $FEV_1$ — % of predicted value | 67.3±23.9 | 65.9±23.9 | 70.0±23.2 |
| Neutrophil elastase in sputum — no. (%)‖ | | | |
| <LLOQ | 18 (21) | 23 (28) | 21 (24) |
| LLOQ to <20 μg/ml | 42 (48) | 28 (34) | 36 (41) |
| ≥20 μg/ml | 24 (28) | 31 (38) | 29 (33) |
| History of COPD — no. (%) | 17 (20) | 12 (15) | 13 (15) |
| History of asthma — no. (%) | 25 (29) | 18 (22) | 21 (24) |

* Plus–minus values are means ±SD. Table S2 provides additional details about the demographic characteristics of the patients. COPD denotes chronic obstructive pulmonary disease, and $FEV_1$ forced expiratory volume in 1 second.
† Race was determined by the investigator.
‡ This characteristic was a stratification criterion.
§ Positivity was defined as a positive *P. aeruginosa* culture at randomization.
¶ Disease severity was classified according to the validated Bronchiectasis Severity Index.[17] Scores range from 0 to 24, with higher scores indicating more severe disease; a score of 0 to 4 indicates mild disease, a score of 5 to 8 moderate disease, and a score of 9 or higher severe disease.
‖ The lower limit of the quantification (LLOQ) on the sputum neutrophil elastase assay was 0.016 μg per milliliter.

longer with brensocatib than with placebo (P=0.03 for the 10-mg brensocatib dose; P=0.04 for the 25-mg brensocatib dose) (Fig. 1A). The results of a sensitivity analysis, which counted the 25 patients who discontinued the trial prematurely as having exacerbation events instead of censoring events, were consistent with those of the primary analysis. The adjusted hazard ratio in the comparison of brensocatib with placebo was 0.58 (95% confidence interval [CI], 0.35 to 0.95) in the 10-mg group (P=0.03) and 0.62 (95% CI, 0.38 to 0.99) in the 25-mg group (P=0.046).

### SECONDARY END POINTS

Over the 24-week treatment period, there were 54 exacerbations in the placebo group, 34 exacerbations in the 10-mg brensocatib group, and 42 exacerbations in the 25-mg brensocatib group. The distribution of symptoms and signs that were identified during exacerbations is shown in Table S3. According to the Cochran–Mantel–Haenszel analysis, the percentage of patients who had one or more exacerbations was significantly lower in each brensocatib group than in the placebo group (placebo: 48% [42 patients]; 10-mg brensocatib: 32% [26 patients], P=0.03 vs. placebo; and 25-mg brensocatib: 33% [29 patients], P=0.04 vs. placebo) (Fig. 1B).

The incidence rates of exacerbations according to trial group were as follows: in the placebo group, 1.37 exacerbations per person-year (95% CI, 1.02 to 1.84); in the 10-mg brensocatib group, 0.88 exacerbations per person-year (95% CI, 0.61 to 1.26); and in the 25-mg brensocatib group, 1.03 exacerbations per person-year (95% CI, 0.75 to 1.42). The incidence-rate ratio for brensocatib as compared with placebo (negative binomial model) was 0.64 (95% CI, 0.42 to 0.98) in the 10-mg group (P=0.04) and 0.75 (95% CI, 0.50 to 1.13) in the 25-mg group (P=0.17). The unadjusted hazard ratio for recurrent exacerbations in the comparison of brensocatib with placebo

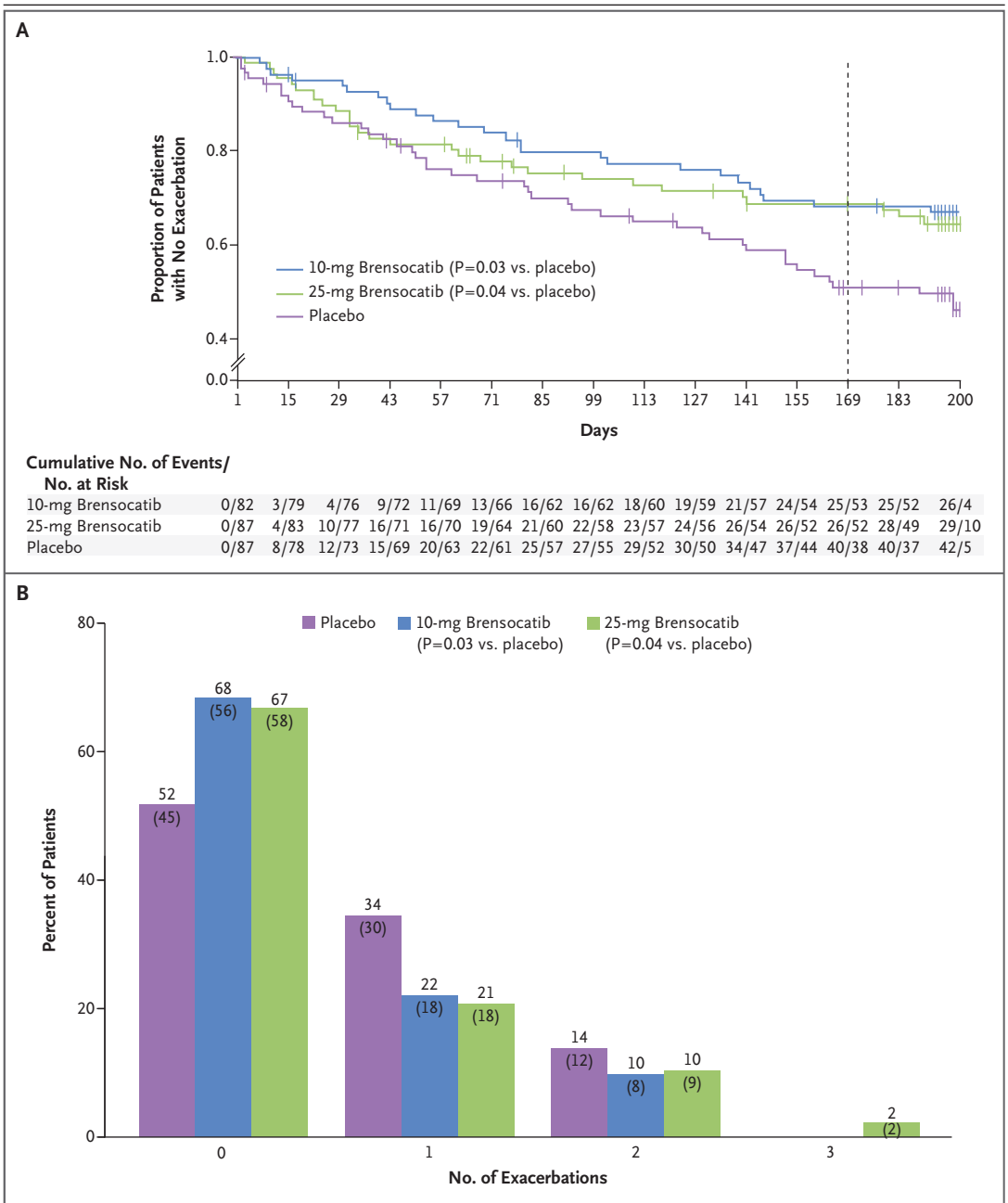


**Figure 1. Time to the First Exacerbation and Patients with No, One, or More Exacerbations (Intention-to-Treat Population).**

Panel A shows a Kaplan–Meier plot of the time to the first exacerbation. Treatment with brensocatib significantly prolonged the time, as compared with placebo, to the first bronchiectasis exacerbation. P values were calculated by the stratified log-rank test. The dashed line at week 24 indicates the end of the treatment period. Tick marks indicate censored data. Panel B shows exacerbations during the treatment period according to trial group. The percentage of patients who had one or more exacerbations was lower with brensocatib than with placebo. The numbers in parentheses indicate the numbers of patients in each trial group who had the specified number of exacerbations. P values were calculated by the Cochran–Mantel–Haenszel test.

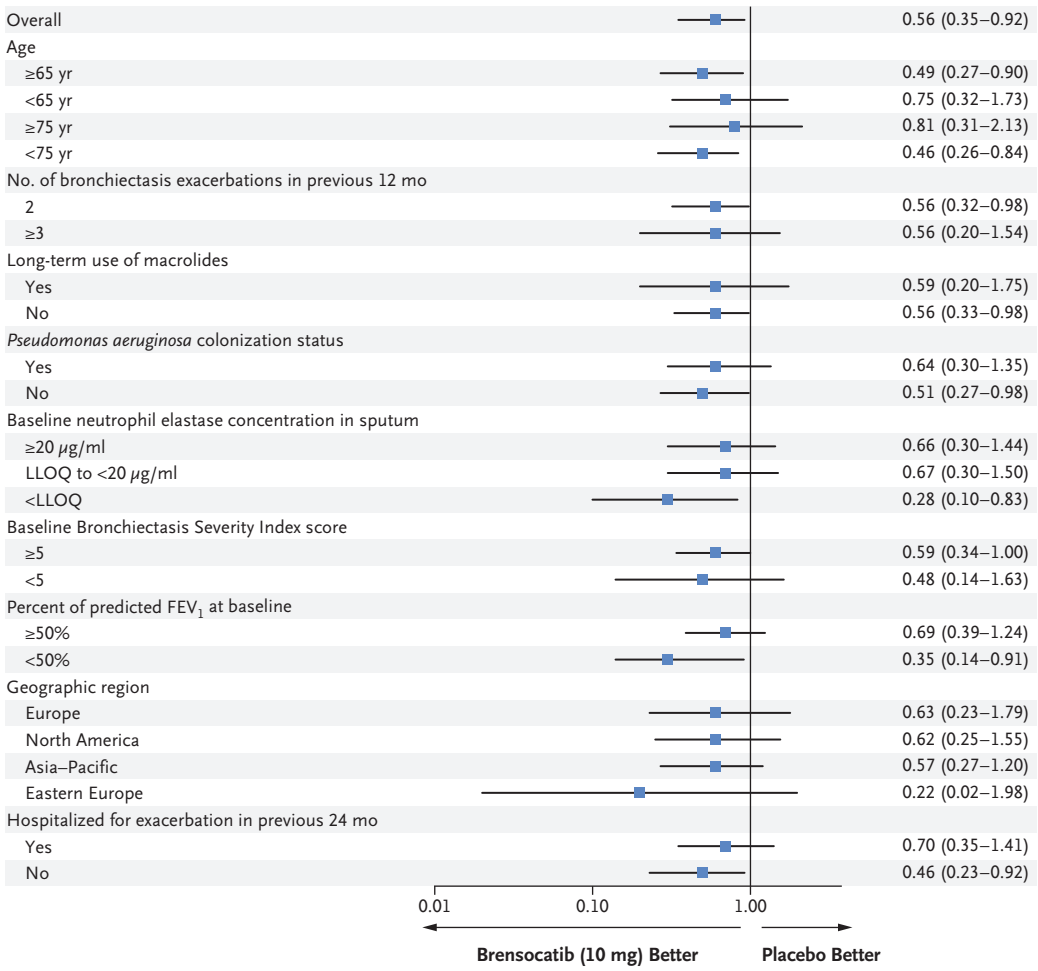


**Figure 2. Time to First Exacerbation, According to Subgroup.**

Shown are subgroups according to receipt of the 10-mg dose of brensocatib or placebo. The time to the first exacerbation was defined as the time (in days) from the date of randomization to the date of the first documented exacerbation. The unadjusted hazard ratio estimates were obtained from the Cox proportional-hazards model. Results for all 23 of the subgroups analyzed are reported. The lower limit of the quantification (LLOQ) on the sputum neutrophil elastase assay was 0.016 μg per milliliter. Scores on the Bronchiectasis Severity Index range from 0 to 24, with higher scores indicating more severe disease; a score of 0 to 4 indicates mild disease, a score of 5 to 8 moderate disease, and a score of 9 or higher severe disease. Europe included all the European countries in the trial (Belgium, Bulgaria, Denmark, Germany, Italy, the Netherlands, Poland, Spain, and the United Kingdom), and Eastern Europe was defined as Bulgaria and Poland. $FEV_1$ denotes forced expiratory volume in 1 second. (Results of the subgroup analysis comparing the 25-mg brensocatib group with the placebo group are shown in Fig. S3.)

(Anderson–Gill model) was 0.65 (95% CI, 0.42 to 0.95) in the 10-mg group (P=0.047) and 0.77 (95% CI, 0.51 to 1.15) in the 25-mg group (P=0.20).

Severe exacerbations were reported in 10 patients in the placebo group, in 5 in the 10-mg brensocatib group, and in 4 in the 25-mg brensocatib group. The unadjusted annualized rate

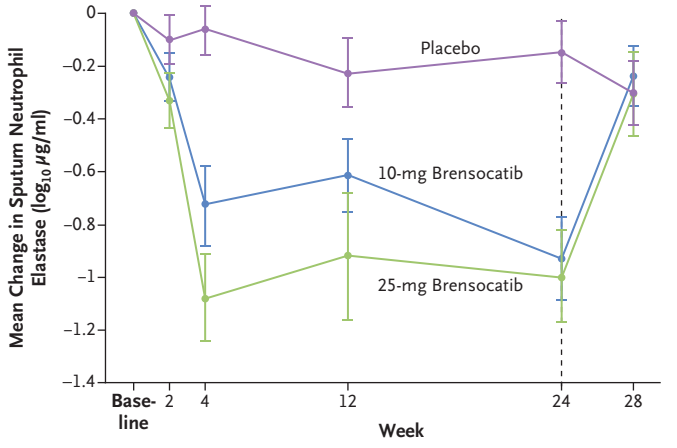


**Figure 3. Mean Change in Sputum Neutrophil Elastase Concentration.**

The mean concentration of neutrophil elastase in sputum was lower in each brensocatib group than in the placebo group from week 2 through week 24. Measurements of active neutrophil elastase were conducted in the pharmacodynamic population, which comprised all the patients who had at least one measurement before receipt of the dose of brensocatib or placebo and one measurement after receipt, with no major protocol deviations. The baseline concentration of neutrophil elastase was derived from the mean values observed during screening and day 1. Log-transformed mean data (reported as $\log_{10}$ μg per milliliter) with standard errors (I bars) are shown. The dashed line at week 24 indicates the end of the treatment period.

of severe exacerbations per person-year was 0.30, 0.19, and 0.11, respectively.

Subgroup analyses yielded point estimates of less than 1.00, as compared with placebo, for the time to the first exacerbation and for the frequency of exacerbations with both brensocatib doses (Fig. 2 and Fig. S3). No meaningful differences in response according to the baseline concentration of neutrophil elastase in sputum were observed between the brensocatib groups and the placebo group, although the study was not powered to detect differences on this end point.

At week 24, the least-squares mean (±SE) change in the percent of the predicted $FEV_1$ after bronchodilator use was −1.8±0.9 percentage points in the placebo group, −0.3±0.9 percentage points in the 10-mg brensocatib group, and −0.3±0.8 percentage points in the 25-mg brensocatib group. The least-squares mean difference, as compared with placebo, in the percent of the predicted $FEV_1$ was 1.5 percentage points (95% CI, −0.7 to 3.6) in the 10-mg brensocatib group and 1.5 percentage points (95% CI, −0.7 to 3.6) in the 25-mg brensocatib group.

The differences in the observed changes from baseline in the score on the Respiratory Symptoms domain of the Quality of Life–Bronchiectasis questionnaire, measured as least-squares mean differences (with higher scores indicating a better quality of life), did not reach the minimally important difference (difference between 10-mg brensocatib and placebo, −2.0 points [95% CI, −3.9 to 0.02]; difference between 25-mg brensocatib and placebo, 0.2 points [95% CI −1.8 to 2.2]). With regard to exploratory health-related quality-of-life assessments, scores on the other domains of the Quality of Life–Bronchiectasis questionnaire are shown in Table S4, scores on the Leicester Cough Questionnaire in Table S5, and scores on the St. George's Respiratory Questionnaire in Table S6.

During the 24-week treatment period, the mean concentrations of neutrophil elastase in sputum were lower with both brensocatib doses than with placebo (Fig. 3). Sputum neutrophil elastase activity returned to baseline values 4 weeks after the end of the treatment period.

### SAFETY

The percentages of patients who had an adverse event during the treatment period that led to the discontinuation of the trial or the discontinuation of brensocatib or placebo were similar across the trial groups (Table 2), with no obvious trends or relationships to treatment. Adverse events during the treatment period were mild to moderate in 64% of the patients receiving placebo, in 88% of those receiving the 10-mg dose of brensocatib, and in 75% of those receiving the 25-mg dose. When exacerbations were excluded, the incidence of severe adverse events during the treatment period was similar across the trial groups. Headache and dyspnea were the only common adverse events (i.e., those reported in ≥10% of the patients in any group) that had a significantly higher incidence in the 25-mg brensocatib group than in the placebo group.

A higher percentage of patients in the placebo group than in the 25-mg brensocatib group had a serious adverse event during the treatment period — a finding that was probably due to the percentage of patients who reported exacerbations as a serious adverse event. One death (due to bronchiectasis progression) occurred in a patient who received the 25-mg dose of brenso-

**Table 2. Safety Analyses.***

| Event | Placebo (N=85) | 10-mg Brensocatib (N=81) | P Value for 10-mg Brensocatib vs. Placebo | 25-mg Brensocatib (N=89) | P Value for 25-mg Brensocatib vs. Placebo |
|---|---|---|---|---|---|
| Any adverse event — no. (%) | 67 (79) | 75 (93) | 0.01 | 74 (83) | 0.47 |
| Any adverse event, excluding bronchiectasis exacerbations — no. (%) | 32 (38) | 51 (63) | 0.001 | 48 (54) | 0.03 |
| Maximum severity of events — no. (%) | | | | | |
| Grade 1: mild | 21 (25) | 27 (33) | 0.22 | 30 (34) | 0.19 |
| Grade 2: moderate | 33 (39) | 44 (54) | 0.04 | 37 (42) | 0.71 |
| Grade 3: severe† | 13 (15) | 3 (4) | 0.01 | 6 (7) | 0.07 |
| Grade 4: life-threatening | 0 | 1 (1) | 0.30 | 0 | NE |
| Grade 5: death | 0 | 0 | NE | 1 (1) | 0.33 |
| Most common adverse events — no. (%)‡ | | | | | |
| Cough | 10 (12) | 15 (19) | 0.22 | 12 (13) | 0.73 |
| Headache | 3 (4) | 8 (10) | 0.10 | 12 (13) | 0.02 |
| Sputum increased | 6 (7) | 9 (11) | 0.36 | 9 (10) | 0.47 |
| Dyspnea | 2 (2) | 3 (4) | 0.61 | 9 (10) | 0.04 |
| Infective exacerbation of bronchiectasis§ | 9 (11) | 5 (6) | 0.31 | 4 (4) | 0.13 |
| Diarrhea | 9 (11) | 5 (6) | 0.31 | 3 (3) | 0.06 |
| Adverse event resulting in discontinuation of placebo or brensocatib — no. (%) | 9 (11) | 6 (7) | 0.48 | 6 (7) | 0.37 |
| Adverse event resulting in trial discontinuation — no. (%) | 3 (4) | 3 (4) | 0.95 | 4 (4) | 0.75 |
| Adverse event of special interest — no. (%) | 23 (27) | 27 (33) | 0.38 | 35 (39) | 0.09 |
| Skin event | 10 (12) | 12 (15) | 0.56 | 21 (24) | 0.04 |
| Dental event | 3 (4) | 13 (16) | 0.01 | 9 (10) | 0.09 |
| Infection | 15 (18) | 11 (14) | 0.47 | 15 (17) | 0.89 |
| Increase of ≥2 mm in periodontal pocket depth — no./total no. (%)¶ | | | | | |
| Regardless of absolute depth | 9/69 (13) | 12/71 (17) | 0.41 | 14/73 (19) | 0.32 |
| With absolute depth of ≥5 mm | 8/69 (12) | 8/71 (11) | 0.92 | 9/73 (12) | 0.88 |
| Serious adverse event — no. (%) | 19 (22) | 11 (14) | 0.14 | 10 (11) | 0.049 |
| Most common serious adverse events — no. (%)‖ | | | | | |
| Infective exacerbation of bronchiectasis§ | 9 (11) | 5 (6) | 0.31 | 4 (4) | 0.13 |
| Pneumonia | 3 (4) | 0 | 0.09 | 4 (4) | 0.75 |

* Shown are adverse events that occurred during the treatment period, which were reported and classified according to terminology from the *Medical Dictionary for Regulatory Activities* (MedDRA). Safety analyses were based on the safety population, which included all 255 patients who received at least one dose of brensocatib or placebo. One patient in the placebo group never received placebo. At one of the trial sites, two patients (one in the placebo group and one in the 10-mg brensocatib group) were incorrectly dispensed 25 mg of brensocatib. P values were calculated by the chi-square test; if there were no events in a group, the P value could not be estimated (NE).

† Severe adverse events, excluding exacerbations, occurred in 4 patients (5%) who received placebo, in 1 patient (1%) who received the 10-mg dose of brensocatib (P=0.19 vs. placebo), and in 5 patients (6%) who received the 25-mg dose (P=0.79 vs. placebo).

‡ The most common adverse events during the treatment period were those reported in at least 10% of the patients in any group.

§ Exacerbations were also reported as adverse events and coded according to MedDRA terminology.

¶ Pocket depth was evaluated at three dental visits (at baseline and at weeks 8 and 24). Shown are data from patients who underwent dental evaluation at baseline and week 24.

‖ The most common serious adverse events during the treatment period were those reported in at least 3% of the patients in any group.

catib. No clinically meaningful trends or changes in electrocardiograms, clinical laboratory values, vital signs, physical examination findings, or pulmonary-function tests after bronchodilator use were observed.

Infection-related adverse events of special interest were evenly distributed across the trial groups (Table 2). The incidence of adverse events of special interest related to skin were higher with the 25-mg dose of brensocatib than with placebo, and those in the dental category were higher with the 10-mg dose of brensocatib than with placebo; none of these events were considered by the investigator to be a serious adverse event. Hyperkeratosis was reported in one patient who received placebo, in three patients who received the 10-mg dose of brensocatib, and in one patient who received the 25-mg dose. All the events resolved or had abated by the end of the trial, and in no case was the use of brensocatib or placebo interrupted. Details regarding adverse events of special interest are provided in Table S7.

Across the trial groups, the numbers of patients with dental sites that had an increase of at least 2 mm in the pocket depth and an absolute depth of at least 5 mm (the threshold of concern in periodontal disease[18]) were evenly distributed, which suggests that there was no difference among the groups in the progression of periodontal disease. Two patients discontinued the trial owing to an adverse event of special interest: one in the placebo group (because of pneumonia) and the other in the 25-mg brensocatib group (because of palmar erythema).

## DISCUSSION

Among patients with bronchiectasis and a history of frequent exacerbations, treatment with brensocatib for 24 weeks significantly prolonged the time to the first exacerbation at both the 10-mg and 25-mg doses and led to a risk of exacerbation over the treatment period that was approximately 40% lower than that with placebo. Annualized rates of exacerbation in the brensocatib groups were lower than the rate in the placebo group (36% lower with the 10-mg dose, and 25% lower with the 25-mg dose). Severe exacerbations accounted for approximately 20% of all the exacerbations in the trial; the number of severe exacerbations in each brensocatib group was half that reported in the placebo group. The results were consistent across subgroups defined according to age, baseline neutrophil elastase concentrations, the number of exacerbations in the 12 months before the trial, the Bronchiectasis Severity Index score, and lung function. Overall, the incidence of adverse events during the treatment period, excluding exacerbations, was higher with either brensocatib dose than with placebo. The incidence of hyperkeratosis and the incidence of increase in the dental pocket depth, which were two skin-related and dental-related adverse events of special interest, were similar across the groups.

The observed decrease in exacerbation frequency among brensocatib-treated patients provides some evidence for neutrophil serine proteases in the pathophysiology of exacerbations of bronchiectasis.[5,19-21] A reduction in neutrophil recruitment has been shown to increase the risk of infection.[22,23] Thus, a reduction in the concentrations of neutrophil proteases by means of DPP-1 antagonism with brensocatib appears to offer clinical benefits without apparently compromising antibacterial defense; however, this trial was short in duration and limited in enrollment, so these findings cannot be considered to be clinically directive. This trial was not sufficiently powered to show differences in efficacy between the two doses of brensocatib that we tested.

A higher incidence of infection with brensocatib than with placebo was not observed in our 6-month trial; however, we do not know whether brensocatib can be given without a long-term increased risk of infection. Although only five cases of hyperkeratosis were reported overall, the limited duration of the treatment period makes conclusions about this side effect difficult.

In this trial, we found that brensocatib prolonged the time to the first exacerbation and led to a lower frequency of exacerbations than placebo in patients with bronchiectasis. These results show the potential clinical benefits of directly reducing inflammation in patients with bronchiectasis. Larger and longer-term trials to investigate the risks and benefits of this approach are now needed.

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