The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 24, 2025 VOL. 392 NO. 16

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

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ABSTRACT

BACKGROUND

In bronchiectasis, neutrophilic inflammation is associated with an increased risk of exacerbations and disease progression. Brensocatib, an oral, reversible inhibitor of dipeptidyl peptidase 1 (DPP-1), targets neutrophil serine proteases, key mediators of neutrophilic inflammation.

METHODS

In a phase 3, double-blind trial, we randomly assigned patients with bronchiectasis (in a 1:1:1 ratio for adults and a 2:2:1 ratio for adolescents) to receive brensocatib (10 mg or 25 mg once per day) or placebo. The primary end point was the annualized rate of adjudicated pulmonary exacerbations over a 52-week period. The secondary end points, listed in hierarchical testing order, were the time to the first exacerbation during the 52-week period; the percentage of patients remaining exacerbation-free at week 52; the change in forced expiratory volume in 1 second (FEV_1); the annualized rate of severe exacerbations; and change in quality of life.

RESULTS

A total of 1721 patients (1680 adults and 41 adolescents) underwent randomization and received brensocatib or placebo. The annualized rate of pulmonary exacerbations was 1.02 in the 10-mg brensocatib group, 1.04 in the 25-mg brensocatib group, and 1.29 in the placebo group (rate ratio, brensocatib vs. placebo, 0.79 [95% confidence interval {CI}, 0.68 to 0.92; adjusted P=0.004] with the 10-mg dose and 0.81 [95% CI, 0.69 to 0.94; adjusted P=0.005] with the 25-mg dose). The hazard ratio for the time to the first exacerbation was 0.81 (95% CI, 0.70 to 0.95; adjusted P=0.02) with the 10-mg dose and 0.83 (95% CI, 0.70 to 0.97; adjusted P=0.04) with the 25-mg dose. In each brensocatib group, 48.5% of patients remained exacerbation-free at week 52, as compared with 40.3% in the placebo group (rate ratio, 1.20 [95% CI, 1.06 to 1.37; adjusted P=0.02] with the 10-mg dose and 1.18 [95% CI, 1.04 to 1.34; adjusted P=0.04] with the 25-mg dose). At week 52, FEV_1 had declined by 50 ml with the 10-mg dose, 24 ml with the 25-mg dose, and 62 ml with placebo (least-squares mean difference vs. placebo, 11 ml [95% CI, –14 to 37; adjusted P=0.38] with the 10-mg dose and 38 ml [95% CI, 11 to 65; adjusted P=0.04] with the 25-mg dose). The incidence of adverse events was similar across groups, except for a higher incidence of hyperkeratosis with brensocatib.

CONCLUSIONS

Among patients with bronchiectasis, once-daily treatment with brensocatib (10 mg or 25 mg) led to a lower annualized rate of pulmonary exacerbations than placebo, and the decline in FEV_1 was less with the 25-mg dose of brensocatib than with placebo. (Funded by Insmed; ASPEN ClinicalTrials.gov number, NCT04594369; EudraCT number, 2020-003688-25.)

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This article was updated on April 24, 2025, at NEJM.org.

N Engl J Med 2025;392:1569-81.
DOI: 10.1056/NEJMoa2411664

CME

Non–cystic fibrosis bronchiectasis (referred to here as bronchiectasis) is a chronic, progressive, inflammatory lung disease with variable clinical manifestations and diverse causes.[1-3] Most patients have a high burden of daily symptoms, including chronic cough and sputum production. Disease exacerbations are associated with decreased health-related quality of life, decreased lung function, and increased all-cause mortality.[1,4-6]

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Neutrophil-mediated inflammation is central to the self-perpetuating cycle of inflammation, impaired mucociliary clearance, structural airway damage, and recurrent infection (collectively known as the vicious vortex) that promotes progression of bronchiectasis.[3] Chronic airway inflammation in bronchiectasis is characterized by excessive release of neutrophil serine proteases, such as neutrophil elastase, which overwhelm endogenous protease inhibitors.[7,8] Neutrophil serine protease precursors are converted to functional enzymes during neutrophil maturation in the bone marrow by dipeptidyl peptidase 1 (DPP-1) and are released during neutrophil activation.[9] In the airway, neutrophil serine proteases promote the vicious vortex and disease progression through the degradation of structural components, including airway elastin, which leads to reduced mucociliary clearance, partly through an increase in mucus hypersecretion, and impaired host defense through the cleavage of antimicrobial peptides and diminished phagocyte function.[10-14] Elevated levels of neutrophil serine proteases in the sputum from patients with bronchiectasis are associated with more severe disease, increased risk of exacerbations, and a more rapid decline in lung function.[10]

A consistent and established standard of care for bronchiectasis is lacking.[15] International guidelines recommend airway clearance techniques, mucoactive agents, and antibiotics for the treatment of infection, but current approaches do not adequately address inflammation or slow disease progression.[16-18]

Brensocatib is an oral, selective, competitive, and reversible inhibitor of DPP-1.[19] In the phase 2 WILLOW trial involving adults with bronchiectasis, treatment with a 10-mg or 25-mg dose of brensocatib, administered once daily for 24 weeks, prolonged the time to the first exacerbation and led to a lower rate of exacerbations than placebo.[20] We conducted an international, phase 3, double-blind, randomized, placebo-controlled trial (ASPEN) involving adult and adolescent patients with bronchiectasis to evaluate the efficacy and safety of 52 weeks of once-daily 10-mg or 25-mg brensocatib added to existing clinical management.

Methods

Trial Design and Patients

Data from 390 trial sites across 35 countries were included in the primary efficacy analysis. Data from 44 patients in Ukraine were not included owing to the ongoing military conflict. Two patients from one U.S. site were excluded owing to considerable noncompliance with Good Clinical Practice guidelines. Eligible patients had a clinical history consistent with bronchiectasis (chronic cough or sputum production or recurrent respiratory tract infections) and a confirmatory computed tomographic scan of the chest within 5 years before screening. Eligible adults were 18 to 85 years of age, had a body-mass index (the weight in kilograms divided by the square of the height in meters) of 18.5 or greater at screening, and had at least two exacerbations that had led to antibiotic treatment in the 12 months before screening. Eligible adolescents were 12 to 17 years of age, had a body weight 30 kg or greater at screening, and had at least one exacerbation that led to antibiotic treatment in the 12 months before screening.

Key exclusion criteria, as verified by a trial site investigator, were chronic obstructive pulmonary disease or asthma if the respiratory symptoms were primarily driven by these diseases (secondary diagnoses of these diseases were allowed); bronchiectasis due to cystic fibrosis; or known or suspected immunodeficiency disorder. Full eligibility criteria and details of the trial design were published previously[21] and are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Trial Oversight

The trial protocol, available at NEJM.org, was developed by the sponsor (Insmed) with input from the steering committee. Data were collected by trial site investigators and analyzed by the sponsor. The manuscript was written by the authors with assistance from a medical writer (funded by Insmed) in accordance with Good

Publication Practice guidelines. The authors critically reviewed all drafts, made the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and adherence to the final protocol. No confidentiality agreements were made that precluded the publication of trial findings.

The trial was conducted in accordance with the principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Council for Harmonisation, and applicable regulatory requirements. The protocol was approved by the institutional review board or independent ethics committee at each trial site. All the patients provided written informed consent.

An independent, external data monitoring committee reviewed all adverse events in an unblinded manner, and an independent clinical end point committee adjudicated all reported exacerbation events in a blinded manner to determine whether they met the protocol definition of an exacerbation and to determine the start and end dates for each event.

TRIAL PROCEDURES

After the screening period, eligible patients were randomly assigned (adults in a 1:1:1 ratio and adolescents in a 2:2:1 ratio) to receive once-daily oral brensocatib (10 mg or 25 mg) or matched placebo for 52 weeks (Fig. S1 in the Supplementary Appendix). Randomization was performed with the use of a central interactive Web-response system. Adults were stratified according to geographic region (North America, Europe, Japan, or the rest of the world), *Pseudomonas aeruginosa*–positive sputum sample at screening (yes or no), and the number of exacerbations (2 or ≥3) in the 12 months before screening; adolescents were not stratified according to these factors. Adherence to brensocatib or placebo was calculated by considering the number of dispensed and returned tablets.

Exacerbations were defined according to modified consensus criteria[22] as the presence of 3 or more of the following symptoms for at least 48 hours that led a physician to prescribe systemic antibiotics: increased cough; increased sputum production or change in sputum consistency; increased sputum purulence; increased breathlessness, decreased exercise tolerance, or both; fatigue, malaise, or both; or hemoptysis. Exacerbations that led to treatment with intravenous antibiotics or hospitalization were considered to be severe.

Adults completed the Respiratory Symptoms domain of the Quality of Life–Bronchiectasis questionnaire[23] at baseline and every 2 weeks through the end of the trial (scores range from 0 to 100, with higher scores indicating fewer symptoms [minimum clinically important difference, 8 points]). Adult patients also completed the Bronchiectasis Exacerbation and Symptoms Tool questionnaire,[24] an electronic diary, each evening from the time of screening through the end of the trial (scores range from 0 to 26, with lower scores indicating fewer symptoms [minimum clinically important difference, 4 points]). If the algorithm that was programmed in the electronic data-capture system detected an increase in symptoms, the trial site and the patient were alerted to a possible pulmonary exacerbation.

END POINTS AND ASSESSMENTS

The primary efficacy end point was the annualized rate (the number of events per year) of adjudicated pulmonary exacerbations during the 52-week treatment period. The secondary efficacy end points, listed in hierarchical testing order, were the time to the first exacerbation during the 52-week treatment period; the percentage of patients remaining exacerbation-free at week 52; the change from baseline in postbronchodilator forced expiratory volume in 1 second (FEV_1) at week 52; the annualized rate of severe exacerbations; and the change from baseline in the score on the Respiratory Symptoms domain of the Quality of Life–Bronchiectasis questionnaire at week 52 (adults only).

Safety was monitored from the time of enrollment through the end of the trial by means of clinical laboratory tests, vital sign measurements, electrocardiography, and assessments of adverse events. An adverse event of special interest was defined as an event that is known to be related to treatment with DPP-1 inhibitors. The inclusion of hyperkeratosis and periodontitis or gingivitis as adverse events of special interest was informed by patients with Papillon–Lefèvre syndrome, a rare genetic disorder in which the near-complete absence of DPP-1 gives rise to these features.[25] Severe infection and pneumonia were additional adverse events of special interest.

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

Characteristic	Brensocatib, 10 mg (N=583)	Brensocatib, 25 mg (N=575)	Placebo (N=563)
Age			
Mean — yr	59.8±15.9	60.6±15.8	60.0±15.4
Distribution — no. (%)			
≥75 yr	83 (14.2)	84 (14.6)	93 (16.5)
18 to 74 yr	483 (82.8)	475 (82.6)	462 (82.1)
<18 yr	17 (2.9)	16 (2.8)	8 (1.4)
Female sex — no. (%)	385 (66.0)	360 (62.6)	362 (64.3)
Race or ethnic group — no. (%)†			
White	431 (73.9)	430 (74.8)	405 (71.9)
Asian	63 (10.8)	64 (11.1)	64 (11.4)
More than one race or ethnic group	25 (4.3)	20 (3.5)	21 (3.7)
American Indian or Alaska Native	8 (1.4)	6 (1.0)	9 (1.6)
Black or African American	2 (0.3)	5 (0.9)	3 (0.5)
Native Hawaiian or Pacific Islander	1 (0.2)	0	1 (0.2)
Other	5 (0.9)	4 (0.7)	1 (0.2)
Unknown or not reported	48 (8.2)	46 (8.0)	59 (10.5)
Body-mass index‡	25.5±5.4	25.4±5.1	25.1±4.9
Most common causes of bronchiectasis — no. (%)§			
Idiopathic or other	331 (56.8)	354 (61.6)	321 (57.0)
Injury: pneumonia or childhood infection	173 (29.7)	156 (27.1)	174 (30.9)
Cilia abnormalities: primary ciliary dyskinesia	47 (8.1)	38 (6.6)	33 (5.9)
Long-term use of antibiotics — no. (%)	146 (25.0)	154 (26.8)	133 (23.6)
Macrolides	110 (18.9)	114 (19.8)	105 (18.7)
Inhaled antibiotics	41 (7.0)	40 (7.0)	36 (6.4)
Use of inhaled glucocorticoids — no. (%)	324 (55.6)	324 (56.3)	352 (62.5)
Pseudomonas aeruginosa–positive sputum sample — no. (%)	203 (34.8)	205 (35.7)	199 (35.3)
Exacerbations in previous 12 mo — no. (%)			
2¶	411 (70.5)	412 (71.7)	396 (70.3)
≥3	172 (29.5)	163 (28.3)	167 (29.7)
Bronchiectasis Severity Index score — points‖	7.1±3.5	7.1±3.6	7.1±3.6
Hospitalized for exacerbation in previous 24 mo — no. (%)	146 (25.0)	133 (23.1)	142 (25.2)
Postbronchodilator FEV_1 — % of predicted value**	74.3±23.4	74.3±24.6	71.9±22.2
Blood eosinophil count — no. (%)			
<300 cells/mm^3	465 (79.8)	461 (80.2)	452 (80.3)
≥300 cells/mm^3	115 (19.7)	111 (19.3)	106 (18.8)
Missing data	3 (0.5)	3 (0.5)	5 (0.9)
History of COPD — no. (%)	77 (13.2)	83 (14.4)	102 (18.1)
History of asthma — no. (%)	101 (17.3)	109 (19.0)	111 (19.7)

Table 1. (Continued.)

Characteristic	Brensocatib, 10 mg (N=583)	Brensocatib, 25 mg (N=575)	Placebo (N=563)
Smoking status — no. (%)††			
Never	419 (71.9)	412 (71.7)	380 (67.5)
Former	164 (28.1)	163 (28.3)	183 (32.5)
QOL-B RSS — points‡‡	59.8±17.0	61.9±17.2	60.0±16.8

* Plus–minus values are means ±SD. All data were collected at visit 2 (before administration of brensocatib or placebo on day 1 [baseline]), except for the baseline blood eosinophil count, for which the most recent nonmissing value (before administration of brensocatib or placebo) was used as the baseline value; if the count at visit 2 was not missing, then it was used as the baseline value; otherwise, the count at screening (visit 1) was used as the baseline value. Positivity for *P. aeruginosa* in a sputum sample was determined on the basis of the sample that was collected at visit 1. All the patients had baseline data for each characteristic unless specified otherwise. COPD denotes chronic obstructive pulmonary disease. Percentages may not total 100 because of rounding.

† Race or ethnic group was reported by the patients. "Other" includes Australian Aboriginal, Brown, Latin, Latino, Maori, Mexican, New Zealand Maori, and Puerto Rican.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ The most common causes of bronchiectasis included those that were documented in at least 5% of patients.

¶ Adolescents could have had one or more exacerbations in the previous 12 months. 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.

‖ Bronchiectasis Severity Index scores range from 0 to 26, 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. Details on how the Bronchiectasis Severity Index score was calculated are provided in the Supplementary Appendix.

** Baseline values of the forced expiratory volume in 1 second (FEV_1) were not available for 4 patients in the 10-mg brensocatib group and for 4 patients in the 25-mg brensocatib group.

†† Current smokers were excluded from the trial.

‡‡ Scores on the Respiratory Symptom domain of the Quality of Life–Bronchiectasis (QOL-B RSS) questionnaire range from 0 to 100, with higher scores indicating fewer symptoms (minimum clinically important difference, 8 points). The 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.

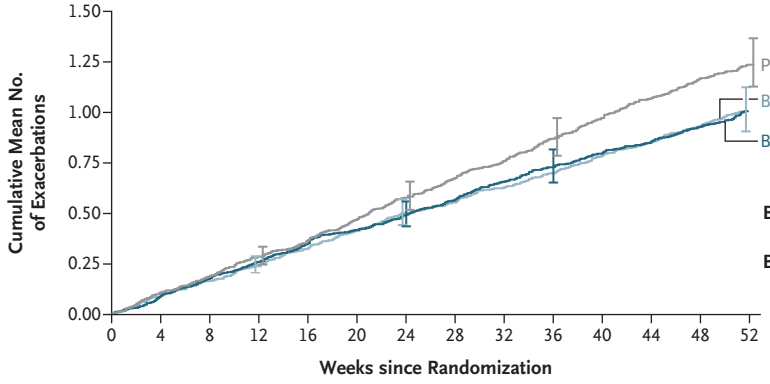
Several preplanned exploratory analyses were conducted. We assessed the annualized rate of exacerbations in prespecified subgroups, the change from baseline in postbronchodilator forced vital capacity at week 52, and the change from baseline in the average daily score on the Bronchiectasis Exacerbation and Symptoms Tool questionnaire over the 52-week treatment period.

STATISTICAL ANALYSIS

Assuming an annualized rate of pulmonary exacerbations of 1.2 events per year in the placebo group, we calculated that a sample of 1620 adults would provide the trial with 90% power to detect a 30% reduction in the rate ratio for an exacerbation at week 52 in either brensocatib group, as compared with the placebo group, with an overall two-sided alpha level of 0.01. We planned to include approximately 40 adolescent patients in the trial to obtain descriptive safety and pharmacokinetic profiles of brensocatib in this age group and to evaluate for a possible directional trend in efficacy.

Efficacy was evaluated in the intention-to-treat population, which included all the patients who had undergone randomization; patients were assessed according to the trial group to which they were assigned. Safety was evaluated in the safety population, which included all the patients who had undergone randomization and received at least one dose of brensocatib or placebo; patients were assessed according to the treatment or placebo received. The data-cutoff date (March 28, 2024) was preplanned to occur when all adults had completed the 52-week treatment period or discontinued the trial early, regardless of whether all adolescents had completed the trial. All patient data collected up to this cutoff date, including data from adolescents who had not yet completed the 52-week treatment period, were included in the primary efficacy end-point and safety analyses.

A Exacerbations over the 52-Wk Treatment Period

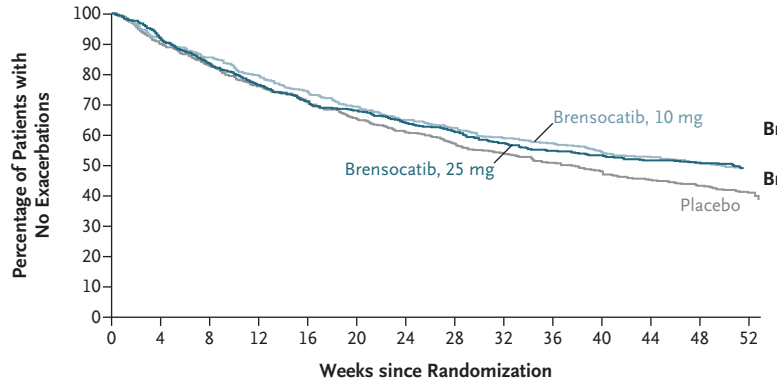


	Rate Ratio vs. Placebo (95% CI)	Adjusted P Value
Brensocatib, 10 mg (N=583)	0.79 (0.68 to 0.92)	0.004
Brensocatib, 25 mg (N=575)	0.81 (0.69 to 0.94)	0.005
Placebo (N=563)	—	—

No. at Risk

Brensocatib, 10 mg	583	582	582	576	570	565	564	555	546	540	533	529	522	516
Brensocatib, 25 mg	575	572	568	566	563	552	550	543	540	537	528	523	520	515
Placebo	563	562	556	551	547	544	539	534	529	522	519	509	507	499

B Time to the First Pulmonary Exacerbation



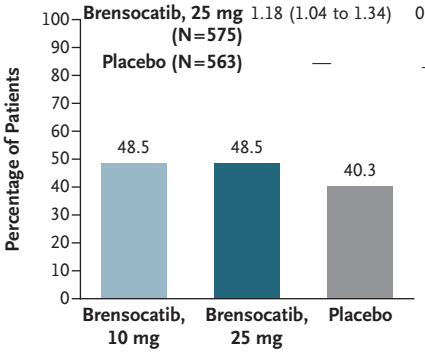
	Hazard Ratio vs. Placebo (95% CI)	Adjusted P Value
Brensocatib, 10 mg (N=583)	0.81 (0.70 to 0.95)	0.02
Brensocatib, 25 mg (N=575)	0.83 (0.70 to 0.97)	0.04
Placebo (N=563)	—	—

No. at Risk

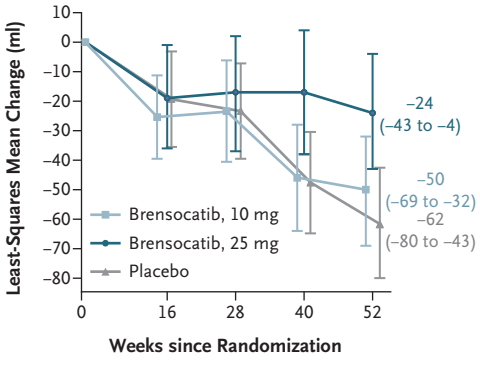
Brensocatib, 10 mg	583	537	498	459	427	393	367	346	322	310	292	280	265	183
Brensocatib, 25 mg	575	526	475	433	400	380	357	337	313	296	282	270	264	169
Placebo	563	506	461	417	386	354	328	303	281	261	245	228	217	154

C Exacerbation-free during the Treatment Period

	Rate Ratio vs. Placebo (95% CI)	Adjusted P Value
Brensocatib, 10 mg (N=583)	1.20 (1.06 to 1.37)	0.02
Brensocatib, 25 mg (N=575)	1.18 (1.04 to 1.34)	0.04
Placebo (N=563)	—	—



D Change in Postbronchodilator FEV_1 from Baseline



Least-Squares Mean Difference vs. Placebo (95% CI)

No. with Data

Brensocatib, 10 mg	579	545	529	513	475
Brensocatib, 25 mg	571	529	523	494	487
Placebo	563	522	513	494	468

Figure 1 (facing page). Exacerbations over the 52-Week Treatment Period, Time to the First Pulmonary Exacerbation, Patients Remaining Exacerbation-free, and Change in Postbronchodilator FEV_1 (Intention-to-Treat Population).

Panel A shows the cumulative mean number of pulmonary exacerbations over the 52-week treatment period according to trial group. I bars indicate 95% confidence intervals. Panel B shows a Kaplan–Meier plot of the time to the first exacerbation. Two-sided P values (brensocatib vs. placebo) were calculated with the use of the Wald test of the Cox proportional-hazards regression model. Panel C shows the percentage of patients who remained exacerbation-free during the treatment period according to trial group. These data are based on multiple imputation, because patients who discontinued brensocatib or placebo or withdrew from the trial early might have had a pulmonary exacerbation had they remained in the trial. The rate ratio for remaining exacerbation-free is reported here, although the odds ratio is the prespecified statistical inference in the statistical analysis plan. The reported P values are based on the odds ratio from the logistic-regression model, as prespecified in the statistical analysis plan, because these P values were used in the hierarchical testing. Panel D shows the least-squares mean change from baseline in the forced expiratory volume in 1 second (FEV_1), which was analyzed with the use of a linear repeated-measures model that included trial group, visit, trial-group-by-visit interaction, age group, and randomization stratification factors (*Pseudomonas aeruginosa*–positive sputum-culture status at screening, the number of exacerbations in the previous 12 months, and geographic region) as fixed effects and the baseline FEV_1 value as a covariate. P values (brensocatib vs. placebo) were calculated on the basis of the Wald test of the logistic-regression model. I bars indicate 95% confidence intervals.

The primary end point was analyzed with the use of a negative binomial model, with trial-group assignment and stratification factors as fixed effects and the logarithm of the time at risk during the trial as an offset variable. All observed exacerbations up to week 52 were included in the main analyses. Missing data due to the withdrawal of patients from the trial before week 52 were assumed to be missing at random and were modeled on the basis of the distribution of observations made during the trial. Sensitivity analyses were performed on the basis of various assumptions regarding event rates after trial withdrawal (see the Supplementary Appendix). P values were adjusted according to an enhanced mixture-based gatekeeping procedure[26] to address multiplicity across the two brensocatib doses and the hierarchy of the primary and five secondary end points. The primary end point was tested at an alpha level of 0.01 and the secondary end points were tested at an alpha level of 0.05. Details on the handling of missing data and other statistical methods are provided in the Supplementary Appendix.

RESULTS

TRIAL POPULATION

From November 2020 through March 2023, a total of 2296 patients underwent screening, of whom 1767 were randomly assigned to a trial group. After the exclusion of 46 patients (Fig. S2 and Table S1), the intention-to-treat population comprised 583 patients in the 10-mg brensocatib group, 575 patients in the 25-mg brensocatib group, and 563 patients in the placebo group. A total of 86.7% of the patients completed the 52-week treatment period. The mean adherence to the assigned regimen was 96.5% in the safety population.

The baseline demographic and clinical characteristics of the patients did not differ substantially across the trial groups (Table 1 and Table S2). The patients were predominantly female (64.3%) and White (73.6%). Approximately one third of the patients (35.3%) had *P. aeruginosa*–positive sputum samples at screening and had at least three exacerbations in the previous 12 months (29.2%); 15.2% of the patients had a history of chronic obstructive pulmonary disease, and 18.7% had a history of asthma. In each of the three trial groups, the median duration of follow-up was 392 days (range, 61 to 504 in the 10-mg brensocatib group; 16 to 469 in the 25-mg brensocatib group; and 15 to 574 in the placebo group), and the median duration of exposure to brensocatib or placebo was 364 days (range, 1 to 418 in the 10-mg brensocatib group; 6 to 402 in the 25-mg brensocatib group; and 6 to 405 in the placebo group).

Among the patients in the 10-mg brensocatib group, the 25-mg brensocatib group, and the placebo group, 17 (2.9%), 16 (2.8%), and 8 (1.4%), respectively, were adolescents, of whom 8, 7, and 4 had completed 52 weeks of treatment by the data-cutoff date. The duration of exposure to brensocatib or placebo among adolescents was 24 weeks or more for 98% and 36 weeks or more for 71%.

PRIMARY END POINT

The annualized rate of adjudicated pulmonary exacerbations was 1.02 (95% confidence interval [CI],

0.91 to 1.13) in the 10-mg brensocatib group, 1.04 (95% CI, 0.93 to 1.16) in the 25-mg brensocatib group, and 1.29 (95% CI, 1.16 to 1.43) in the placebo group (Fig. 1A and Table 2). The rate ratios in the 10-mg and 25-mg brensocatib groups, as compared with the placebo group, were 0.79 (95% CI, 0.68 to 0.92; adjusted P=0.004) and 0.81 (95% CI, 0.69 to 0.94; adjusted P=0.005), respectively.

SECONDARY END POINTS

The hazard ratio (brensocatib vs. placebo) for the time to the first exacerbation during the 52-week treatment period was 0.81 (95% CI, 0.70 to 0.95; adjusted P=0.02) with the 10-mg dose and 0.83 (95% CI, 0.70 to 0.97; adjusted P=0.04) with the 25-mg dose (Fig. 1B and Table 2), indicating a reduction of 19% and 17%, respectively, in the incidence of the first exacerbation across the 52-week period, as compared with placebo. In each brensocatib group, 48.5% of the patients remained exacerbation-free at week 52 (283 of 583 patients in the 10-mg group and 279 of 575 patients in the 25-mg group), as compared with 40.3% (227 of 563 patients) in the placebo group (rate ratio for remaining exacerbation-free at week 52 [brensocatib vs. placebo], 1.20 [95% CI, 1.06 to 1.37; adjusted P=0.02] with the 10-mg dose and 1.18 [95% CI, 1.04 to 1.34; adjusted P=0.04] with the 25-mg dose) (Fig. 1C).

At week 52, the postbronchodilator FEV_1 had declined from baseline by a mean (±SE) of 50±9 ml in the 10-mg brensocatib group, 24±10 ml in the 25-mg brensocatib group, and 62±9 ml in the placebo group (least-squares mean difference between brensocatib and placebo, 11 ml [95% CI, −14 to 37; adjusted P=0.38] with the 10-mg dose and 38 ml [95% CI, 11 to 65; adjusted P=0.04] with the 25-mg dose) (Fig. 1D). No further statistical testing of the results from the 10-mg brensocatib group was performed, according to the hierarchical testing procedure.

Table 2. Primary and Secondary End Points (Intention-to-Treat Population).*

End Point	Brensocatib, 10 mg (N=583)	Brensocatib, 25 mg (N=575)	Placebo (N=563)
Primary end point			
Annualized rate of pulmonary exacerbations — no. of events/yr (95% CI)	1.02 (0.91 to 1.13)	1.04 (0.93 to 1.16)	1.29 (1.16 to 1.43)
Rate ratio (95% CI)	0.79 (0.68 to 0.92)	0.81 (0.69 to 0.94)	—
Adjusted P value	0.004	0.005	—
Secondary end points			
Hazard ratio for the time to the first exacerbation during the treatment period (95% CI)	0.81 (0.70 to 0.95)	0.83 (0.70 to 0.97)	—
Adjusted P value	0.02	0.04	—
Exacerbation-free during the treatment period — no. (%)†	283 (48.5)	279 (48.5)	227 (40.3)
Rate ratio for remaining exacerbation-free at week 52 (95% CI)‡	1.20 (1.06 to 1.37)	1.18 (1.04 to 1.34)	—
Adjusted P value§	0.02	0.04	—
Postbronchodilator FEV_1			
LS mean change from baseline to wk 52 — ml¶	−50±9	−24±10	−62±9
LS mean difference vs. placebo (95% CI) — ml	11 (−14 to 37)	38 (11 to 65)	—
Adjusted P value	0.38	0.04	—
Annualized rate of severe exacerbations (95% CI) — no. of events/yr	0.14 (0.10 to 0.18)	0.14 (0.11 to 0.18)	0.19 (0.14 to 0.24)
Rate ratio (95% CI)	0.74 (0.51 to 1.09)	0.74 (0.52 to 1.06)	—
Adjusted P value	NA	0.21	—

Table 2. (Continued.)

End Point	Brensocatib, 10 mg (N=583)	Brensocatib, 25 mg (N=575)	Placebo (N=563)
QOL-B RSS			
LS mean change from baseline to wk 52 — points‖	6.84±0.77	8.58±0.76	4.81±0.75
LS mean difference vs. placebo (95% CI) — points	2.03 (–0.08 to 4.14)	3.77 (1.68 to 5.85)	—

* Plus–minus values are means (±SE). Efficacy was evaluated in the intention-to-treat population, which included all the patients who had undergone randomization; patients were assessed according to the trial group to which they were assigned. The secondary end points are listed in the order in which they were hierarchically tested. No P values are included after the hierarchy was broken (i.e., after the analysis of FEV_1 for the 10-mg dose of brensocatib and after the analysis of severe exacerbations for the 25-mg dose of brensocatib). P values were adjusted for multiplicity and were calculated with the use of the enhanced mixture-based gatekeeping procedure. The primary end point was tested at two-sided alpha level of 0.01 with the use of the truncated Hochberg procedure, with a truncation fraction of 0.9. Secondary end points were tested at two-sided alpha level of 0.05. Rate ratios and hazard ratios are given for each brensocatib group as compared with the placebo group. FEV_1 denotes forced expiratory volume in 1 second, LS least-squares, NA not applicable, and QOL-B RSS Respiratory Symptom domain score of the Quality of Life–Bronchiectasis.

† Patients were considered to be exacerbation-free if they completed 52 weeks of the trial and had no protocol-defined pulmonary exacerbation, as determined by the independent adjudication committee, or if they discontinued the trial earlier than week 52 and had no pulmonary exacerbation, as confirmed through the adjudication process, and had their response status imputed over a period of at least 365 days. Analyses were based on 100 logistic-regression models that included trial group, sputum sample status at the screening visit (positive or negative for *Pseudomonas aeruginosa*), the number of pulmonary exacerbations (2 or ≥3) in the previous 12 months, stratification region (North America, Europe, Japan, or the rest of the world), and age group (adult or adolescent) as fixed effects. The parameter estimates used in the models were combined according to Rubin's rules and then exponentiated to show the odds ratio.

‡ The rate ratio for remaining exacerbation-free at week 52 is reported here, although the odds ratio is the prespecified statistical inference in the statistical analysis plan.

§ The P values reported here 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.

¶ In this end-point analysis, the baseline values were covariates and were adjusted for; therefore, patients without baseline data or complete measurements (19 patients in the 10-mg brensocatib group, 24 patients in the 25-mg brensocatib group, and 24 patients in the placebo group) were excluded.

‖ This end-point analysis included adult patients only. The baseline values were covariates and were adjusted for; therefore, patients without baseline data or complete measurements (79 of 566 adults in the 10-mg brensocatib group, 64 of 559 adults in the 25-mg brensocatib group, and 69 of 555 adults in the placebo group) were excluded.

The annualized rate of severe exacerbations was 0.14 (95% CI, 0.10 to 0.18) in the 10-mg brensocatib group, 0.14 (95% CI, 0.11 to 0.18) in the 25-mg brensocatib group, and 0.19 (95% CI, 0.14 to 0.24) in the placebo group (rate ratios [brensocatib vs. placebo], 0.74 [95% CI, 0.51 to 1.09] with the 10-mg dose and 0.74 [95% CI, 0.52 to 1.06; adjusted P=0.21] with the 25-mg dose). No further statistical testing of the results from the 25-mg brensocatib group was performed, according to the hierarchical testing procedure.

The percentage of patients (adults only) who completed the Respiratory Symptoms domain of the Quality of Life–Bronchiectasis questionnaire was similar across trial groups (>80% at assessment time points). The least-squares mean change from baseline in the score on the Respiratory Symptoms domain of the Quality of Life–Bronchiectasis questionnaire at week 52 was 6.84±0.77 points in the 10-mg brensocatib group, 8.58±0.76 points in the 25-mg brensocatib group, and 4.81±0.75 points in the placebo group (Fig. S3).

The results of prespecified subgroup analyses of the annualized rate of exacerbations are provided in Figure S4 and appeared to be generally consistent with the results in the overall population at both brensocatib doses. Changes from baseline in forced vital capacity and the score on the Bronchiectasis Exacerbation and Symptoms Tool diary at week 52 (exploratory end points) are provided in Table S3 and Figures S5 and S6. The results of the hierarchical testing and the sensitivity and tipping-point analyses are provided in Table 2 and Tables S4 and S5.

SAFETY

The incidence of adverse events overall and of adverse events leading to discontinuation of

brensocatib or placebo or withdrawal from the trial was similar across groups (Table 3 and Tables S6 and S7). The most common adverse events that occurred more frequently with either dose of brensocatib than placebo were coronavirus disease 2019 (Covid-19), nasopharyngitis, cough, and headache. Serious adverse events were reported in 101 patients (17.4%) in the 10-mg brensocatib group, 97 patients (16.9%) in the 25-mg brensocatib group, and 108 patients (19.2%) in the placebo group; adverse events resulting in death occurred in 3 patients (0.5%), 4 patients (0.7%), and 7 patients (1.2%), respectively.

Adverse events of special interest, as reported by the investigators, occurred in 42 patients (7.2%) in the 10-mg brensocatib group, 56 patients (9.8%) in the 25-mg brensocatib group, and 53 patients (9.4%) in the placebo group. Pneumonia was the most common adverse event of special interest and occurred more frequently with placebo (in 5.9% of patients) than with the 10-mg dose (in 4.0%) or 25-mg dose (in 4.7%) of brensocatib. Severe infection was reported in 4 patients (0.7%) in the 10-mg brensocatib group and the placebo group and in 7 patients (1.2%) in the 25-mg brensocatib group. Hyperkeratosis was reported in 8 patients (1.4%) in the 10-mg brensocatib group, 17 patients (3.0%) in the 25-mg brensocatib group, and 4 patients (0.7%) in the placebo group. All but 1 case of hyperkeratosis were mild or moderate and resolved during the trial period; the exception led to treatment discontinuation in 1 patient in the 25-mg brensocatib group.

DISCUSSION

The characteristics of the patients in the ASPEN trial, a large international clinical trial involving more than 1700 patients with bronchiectasis who were enrolled across five continents, were consistent with those of patients included in large bronchiectasis registries (Table S8).[15,21,27] In this trial, brensocatib led to a significantly lower annualized rate of pulmonary exacerbations than placebo, an effect that appeared to be consistent across multiple prespecified subgroups. The time to the first exacerbation was longer and the percentage of patients remaining exacerbation-free was higher with both the 10-mg and 25-mg doses of brensocatib than with placebo. Patients who received the 25-mg dose of brensocatib showed a significantly slower decline in lung function, as measured by FEV_1, over the course of 52 weeks, an effect not seen with the 10-mg dose of brensocatib. These results show that inhibiting DPP-1 with brensocatib — and thereby targeting neutrophilic inflammation — results in meaningful improvements in outcomes in patients with bronchiectasis.

Bronchiectasis is a progressive disease, and frequent exacerbations are critical events associated with decline in lung function, worse quality of life, and premature death from any cause.[1,4-6] No available interventions have been shown to slow the decline in lung function, and the burden of exacerbations remains high, with most patients having two or more exacerbations per year.[15,28] In our trial, brensocatib, when added to patients' existing treatment, was shown to have a clinically meaningful effect on the burden of exacerbations in this patient population. The additional effect of the 25-mg dose of brensocatib on slowing the decline in lung function may be related to improved mucus properties or diminished airway inflammation. Slowing the decline in lung function is important, because the level of lung function is strongly associated with increased morbidity and mortality among patients with bronchiectasis.[29]

Overall, adverse events, adverse events leading to discontinuation of brensocatib or placebo, and serious adverse events during the treatment period were relatively similar across the trial groups. No increase was observed in the incidence of bacterial infections, even with the longer duration of brensocatib exposure (52 weeks in the ASPEN trial, as compared with 24 weeks in the phase 2 WILLOW trial[20]). The incidence of hyperkeratosis was higher with the higher dose of brensocatib. The cases were infrequent and generally mild in severity, and all cases resolved, including one case that led to discontinuation of brensocatib.

The ASPEN trial was conducted during and after the peak of the Covid-19 pandemic. The case mix of patients who presented to the clinic during the pandemic may have tended to be more severely ill to risk going to the clinic than the case mix of patients who presented before

Table 3. Safety Analyses.*

Event	Brensocatib, 10 mg (N=582)	Brensocatib, 25 mg (N=574)	Placebo (N=563)
		number (percent)	
Any adverse event	452 (77.7)	440 (76.7)	448 (79.6)
Severe adverse event	74 (12.7)	67 (11.7)	90 (16.0)
Adverse event determined by an investigator to be related to brensocatib or placebo	72 (12.4)	85 (14.8)	73 (13.0)
Serious adverse event†	101 (17.4)	97 (16.9)	108 (19.2)
Serious adverse event determined by an investigator to be related to brensocatib or placebo	0	1 (0.2)	0
Adverse event resulting in death‡	3 (0.5)	4 (0.7)	7 (1.2)
Adverse event leading to discontinuation of brensocatib or placebo	25 (4.3)	22 (3.8)	23 (4.1)
Adverse event leading to trial withdrawal	14 (2.4)	16 (2.8)	16 (2.8)
Most common adverse events§			
Covid-19	92 (15.8)	120 (20.9)	89 (15.8)
Nasopharyngitis	45 (7.7)	36 (6.3)	43 (7.6)
Cough	41 (7.0)	35 (6.1)	36 (6.4)
Headache	39 (6.7)	49 (8.5)	39 (6.9)
Most common serious adverse events¶			
Bronchiectasis‖	47 (8.1)	48 (8.4)	67 (11.9)
Pneumonia	11 (1.9)	13 (2.3)	16 (2.8)
Any adverse event of special interest**	42 (7.2)	56 (9.8)	53 (9.4)
Hyperkeratosis	8 (1.4)	17 (3.0)	4 (0.7)
Periodontitis or gingivitis	8 (1.4)	12 (2.1)	15 (2.7)
Severe infection	4 (0.7)	7 (1.2)	4 (0.7)
Pneumonia	23 (4.0)	27 (4.7)	33 (5.9)

* Shown are adverse events that occurred from the date of the first dose of brensocatib or placebo through 28 days after the last dose. Adverse events were coded according to preferred terms with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA), version 27.0. Safety was evaluated in the safety population, which included all the patients who had undergone randomization and received at least one dose of brensocatib or placebo; patients were assessed according to the treatment or placebo received. Covid-19 denotes coronavirus disease 2019.

† A serious adverse event was defined as any untoward medical occurrence that, at any dose, resulted in death, was life-threatening, led to inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was an important medical event.

‡ Adverse events resulting in death were aspergillus infection, acute respiratory failure, and bronchiectasis in one patient each in the 10-mg brensocatib group; pneumonia, myocardial infarction, general physical health deterioration, and road traffic accident in one patient each in the 25-mg brensocatib group; and pneumonia, acute respiratory failure, bronchiectasis, hemoptysis, cardiac arrest, cardiorespiratory arrest, and cervical vertebral fracture in one patient each in the placebo group.

§ The most common adverse events during the treatment period were those that were reported in at least 5% of the patients in any group, with a higher incidence in either of the brensocatib groups than in the placebo group.

¶ The most common serious adverse events during the treatment period were those that were reported in at least 2% of the patients in any group.

‖ Bronchiectasis is the preferred term according to version 27.0 of MedDRA; all reported cases were pulmonary exacerbations.

** Hyperkeratosis and periodontitis or gingivitis were of special interest with respect to brensocatib treatment because of their presence in the Papillon–Lefèvre syndrome, which is characterized by mutations in *DPP1* and near-complete loss of DPP-1 function.[25]

the pandemic. However, the annualized rate of exacerbations in the placebo group in this trial was similar to that in the placebo group in the WILLOW trial, which was completed before the pandemic. The estimation of effects and safety were assessed in the overall trial population, which included both adults and adolescents. Although consistency in outcomes was seen between adolescent patients, who were enrolled in the trial with agreement from regulatory authorities, and the overall trial population, the subpopulation of adolescents was limited in size. Similarly, the current trial was powered to detect treatment differences in the overall trial population but was not sized to make firm conclusions with regard to smaller, prespecified subgroups.

Our trial showed that treatment with brensocatib led to a lower annualized rate of exacerbations than placebo in patients with bronchiectasis, and the decline in lung function was less with the 25-mg dose of brensocatib than with placebo.

Supported by Insmed.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank all the patients who participated in the trial and their family members and caregivers, as well as the clinical research teams and support staff at the trial sites for providing patient care and for their contributions to this trial; Harm Tiddens, M.D., Ph.D., and Federico Mollica, B.M., for their contributions in analyzing the computed tomographic scanning data; and Lynsey Fettig, Ph.D., of Envision Pharma Group, for medical writing support.

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REFERENCES

1. Aliberti S, Goeminne PC, O'Donnell AE, et al. Criteria and definitions for the radiological and clinical diagnosis of bronchiectasis in adults for use in clinical trials: international consensus recommendations. Lancet Respir Med 2022;10:298-306.
2. Choi H, McShane PJ, Aliberti S, Chalmers JD. Bronchiectasis management in adults: state of the art and future directions. Eur Respir J 2024;63(6):2400518.
3. Flume PA, Chalmers JD, Olivier KN. Advances in bronchiectasis: endotyping, genetics, microbiome, and disease heterogeneity. Lancet 2018;392:880-90.
4. Chalmers JD, Aliberti S, Filonenko A, et al. Characterization of the "frequent exacerbator phenotype" in bronchiectasis. Am J Respir Crit Care Med 2018;197:1410-20.
5. Chalmers JD, Chang AB, Chotirmall SH, Dhar R, McShane PJ. Bronchiectasis. Nat Rev Dis Primers 2018;4:45.
6. Lapinel N, Choate R, Aksamit T, et al. Characteristics of frequent exacerbators in the US Bronchiectasis and NTM Research Registry (BRR). Eur Respir J 2022;60:Suppl 66:2199. abstract.
7. Gramegna A, Aliberti S, Sibila O, et al. Sputum neutrophil elastase in bronchiectasis: a southern European cohort study. Eur Respir J 2020;56(6):2001702.
8. Keir HR, Shoemark A, Dicker AJ, et al. Neutrophil extracellular traps, disease severity, and antibiotic response in bronchiectasis: an international, observational, multicohort study. Lancet Respir Med 2021;9:873-84.
9. Palmér R, Mäenpää J, Jauhiainen A, et al. Dipeptidyl peptidase 1 inhibitor AZD7986 induces a sustained, exposure-dependent reduction in neutrophil elastase activity in healthy subjects. Clin Pharmacol Ther 2018;104:1155-64.
10. Chalmers JD, Moffitt KL, Suarez-Cuartin G, et al. Neutrophil elastase activity is associated with exacerbations and lung function decline in bronchiectasis. Am J Respir Crit Care Med 2017;195:1384-93.
11. Cheetham CJ, McKelvey MC, McAuley DF, Taggart CC. Neutrophil-derived proteases in lung inflammation: old players and new prospects. Int J Mol Sci 2024;25:5492.
12. Fuschillo S, De Felice A, Balzano G. Mucosal inflammation in idiopathic bronchiectasis: cellular and molecular mechanisms. Eur Respir J 2008;31:396-406.
13. Roghanian A, Drost EM, MacNee W, Howie SEM, Sallenave J-M. Inflammatory lung secretions inhibit dendritic cell maturation and function via neutrophil elastase. Am J Respir Crit Care Med 2006;174:1189-98.
14. Vandivier RW, Fadok VA, Hoffmann PR, et al. Elastase-mediated phosphatidylserine receptor cleavage impairs apoptotic cell clearance in cystic fibrosis and bronchiectasis. J Clin Invest 2002;109:661-70.

15. Chalmers JD, Polverino E, Crichton ML, et al. Bronchiectasis in Europe: data on disease characteristics from the European Bronchiectasis Registry (EMBARC). Lancet Respir Med 2023;11:637-49.
16. Hill AT, Sullivan AL, Chalmers JD, et al. British Thoracic Society guideline for bronchiectasis in adults. Thorax 2019;74: Suppl 1:1-69.
17. Mukae H, Kaneko T, Obase Y, et al. The Japanese Respiratory Society guidelines for the management of cough and sputum (digest edition). Respir Investig 2021;59:270-90.
18. Polverino E, Goeminne PC, McDonnell MJ, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J 2017; 50(3):1700629.
19. Doyle K, Lönn H, Käck H, et al. Discovery of second generation reversible covalent DPP1 inhibitors leading to an oxazepane amidoacetonitrile based clinical candidate (AZD7986). J Med Chem 2016;59:9457-72.
20. Chalmers JD, Haworth CS, Metersky ML, et al. Phase 2 trial of the DPP-1 inhibitor brensocatib in bronchiectasis. N Engl J Med 2020;383:2127-37.
21. Chalmers JD, Burgel P-R, Daley CL, et al. Brensocatib in non-cystic fibrosis bronchiectasis: ASPEN protocol and baseline characteristics. ERJ Open Res 2024; 10(4):00151-2024.
22. Hill AT, Haworth CS, Aliberti S, et al. Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. Eur Respir J 2017;49(6): 1700051.
23. Quittner AL, O'Donnell AE, Salathe MA, et al. Quality of Life Questionnaire–Bronchiectasis: final psychometric analyses and determination of minimal important difference scores. Thorax 2015;70:12-20.
24. Artaraz A, Crichton ML, Finch S, et al. Development and initial validation of the Bronchiectasis Exacerbation and Symptom Tool (BEST). Respir Res 2020; 21:18.
25. Hart TC, Hart PS, Bowden DW, et al. Mutations of the cathepsin C gene are responsible for Papillon–Lefèvre syndrome. J Med Genet 1999;36:881-7.
26. Kordzakhia G, Brechenmacher T, Ishida E, Dmitrienko A, Zheng WW, Li DF. An enhanced mixture method for constructing gatekeeping procedures in clinical trials. J Biopharm Stat 2018;28:113-28.
27. Aksamit TR, O'Donnell AE, Barker A, et al. Adult patients with bronchiectasis: a first look at the US Bronchiectasis Research Registry. Chest 2017;151:982-92.
28. Flume PA, Feliciano J, Lucci M, et al. Pulmonary exacerbations in insured patients with bronchiectasis over 2 years. ERJ Open Res 2023;9(4):00021-2023.
29. Loebinger MR, Wells AU, Hansell DM, et al. Mortality in bronchiectasis: a long-term study assessing the factors influencing survival. Eur Respir J 2009;34: 843-9.