Brensocatib in non-cystic fibrosis bronchiectasis: ASPEN protocol and baseline characteristics

James D. Chalmers[1], Pierre-Régis Burgel[2], Charles L. Daley[3], Anthony De Soyza[4], Charles S. Haworth[5], David Mauger[6], Kevin Mange[7], Ariel Teper[7], Carlos Fernandez[7], Dan Conroy[7] and Mark Metersky[8]

[1]Division of Molecular and Clinical Medicine, University of Dundee, Dundee, UK. [2]Hôpital Cochin and Cystic Fibrosis National Reference Center, Service de Pneumologie, AP-HP and Université Paris-Cité, Inserm U1016-Institut Cochin, Paris, France. [3]National Jewish Health and the University of Colorado, Denver, CO, USA. [4]Population and Health Sciences Institute, NIHR Biomedical Research Centre for Aging Newcastle University and Department of Respiratory Medicine, Newcastle upon Tyne NHS Foundation Trust, Newcastle upon Tyne, UK. [5]Royal Papworth Hospital NHS Foundation Trust and University of Cambridge, Cambridge, UK. [6]Pennsylvania State University, Hershey, PA, USA. [7]Insmed Incorporated, Bridgewater, NJ, USA. [8]University of Connecticut School of Medicine, Farmington, CT, USA.

Corresponding author: James D. Chalmers (j.chalmers@dundee.ac.uk)

Shareable abstract (@ERSpublications)
The phase 3 ASPEN trial enrolled adults with bronchiectasis and a history of exacerbations. This paper outlines the trial design, and reveals that baseline characteristics and treatment patterns were representative of a global bronchiectasis population. https://bit.ly/3vu7RyR

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Abstract

Introduction Brensocatib is an investigational, oral, reversible inhibitor of dipeptidyl peptidase-1 shown to prolong time to first exacerbation in adults with bronchiectasis. Outlined here are the clinical trial design, and baseline characteristics and treatment patterns of adult patients enrolled in the phase 3 ASPEN trial (NCT04594369).

Methods The ASPEN trial is a global study enrolling patients with a clinical history consistent with bronchiectasis (cough, chronic sputum production and/or recurrent respiratory infections), diagnosis confirmed radiologically and ⩾2 exacerbations in the prior 12 months. It was designed to evaluate the impact of two brensocatib doses (10 mg and 25 mg) on exacerbation rate over a 52-week treatment period *versus* placebo. Comprehensive clinical data, including demographics, disease severity, lung function, *Pseudomonas aeruginosa* status and quality of life, were collected at baseline.

Results 1682 adults from 35 countries were randomised from December 2020 to March 2023. Mean age was 61.3 years and 64.7% were female. ∼70% had moderate-to-severe Bronchiectasis Severity Index (BSI) scores, 29.3% had ⩾3 exacerbations in the prior 12 months and 35.7% were positive for *P. aeruginosa*. Mean BSI scores were highest in Australia/New Zealand (8.3) and lowest in Latin America (5.9). Overall, the most common aetiology was idiopathic (58.4%). In *P. aeruginosa*-positive *versus P. aeruginosa*-negative patients, lung function was lower, with greater long-term macrolide (21.5% *versus* 14.0%) and inhaled corticosteroid use (63.5% *versus* 53.9%). There was wide regional variation in long-term antibiotic use in patients with bronchiectasis and *P. aeruginosa*.

Discussion ASPEN baseline characteristics and treatment profiles were representative of a global bronchiectasis population.

Introduction

Non-cystic fibrosis bronchiectasis (hereafter bronchiectasis) is a chronic and progressive inflammatory disease marked by irreversible bronchial dilatation. Once considered an orphan disease [1], bronchiectasis remains a widely neglected respiratory condition, despite its increased prevalence in recent years [2]. Patients with bronchiectasis suffer from daily cough, sputum production [3], recurrent respiratory infections, and exacerbations that may be severe and lead to hospitalisation [4]. Exacerbations are critical

drivers of disease progression and patient burden [5, 6]. Approximately half of patients with bronchiectasis have two or more exacerbations annually [7]. Both the severity and the frequency of exacerbations are associated with worse quality of life, daily symptoms, lung function decline and all-cause mortality [8].

Bronchiectasis is a heterogeneous disease with multiple different underlying causes, and with variable clinical presentations and severity. Recent reports from international registries, including the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC), highlight the diverse range of aetiologies and marked geographical variation in microbiology, severity and outcomes [7, 9–11]. This heterogeneity has been cited as a key challenge in clinical management of the disease [12].

Although these patients use several available therapies, there are currently no pharmacological therapies specifically indicated for the treatment of bronchiectasis approved by the US Food and Drug Administration or the European Medicines Agency and no consistent, established standard of care. Given the dearth of high-quality evidence, international guidelines are based predominantly on low-quality evidence and expert opinion [8]. Management often focuses on the use of airway clearance, mucoactive agents and antibiotics for acute exacerbations [8, 13, 14]. Long-term antibiotics (inhaled or oral (macrolides)) are recommended for patients with three or more exacerbations annually, but are not suitable for all patients and are associated with the development of drug-resistant pathogens [8, 15].

Inflammation, predominantly driven by neutrophils, is central to the "vicious vortex" concept of the pathophysiology of bronchiectasis [12, 16, 17]. Neutrophilic inflammation is believed to drive excess mucus production and secretion, impaired mucociliary clearance, impaired host defence against bacteria and airway remodelling, thereby linking to each of the key components of the disease [16]. Neutrophil serine proteases (NSPs), including neutrophil elastase (NE), are believed to be key mediators of neutrophil-related airway disease [17]. Elevated NE activity in patients with bronchiectasis is correlated with a shortened time to exacerbation and with poor health-related quality of life (QoL) [18]. Dipeptidyl peptidase 1 (DPP-1, also-called cathepsin C) activates NSPs during neutrophil maturation in the bone marrow. Recently, DPP-1 inhibition has been hypothesised to be a potential intervention in diseases mediated by neutrophilic inflammation such as bronchiectasis by reducing the activity of NSPs [19]. Brensocatib is an investigational, oral, selective, competitive, reversible inhibitor of DPP-1 in development for the treatment of bronchiectasis. In the phase 2 WILLOW trial in adults with bronchiectasis, treatment with 10 mg or 25 mg of brensocatib daily *versus* placebo for 24 weeks reduced NE activity in sputum and prolonged the time to first exacerbation. Most adverse events (AEs) reported in the trial were mild to moderate, with similar incidence across treatment groups of severe AEs and AEs leading to discontinuation [19].

The ASPEN phase 3 trial (ClinicalTrials.gov identifier: NCT04594369; EudraCT number: 2020–003688-25) is a global study that has enrolled over 1600 patients with bronchiectasis making it the largest trial conducted in patients with bronchiectasis to date. The primary objective of this study is to evaluate the impact of brensocatib on the rate of bronchiectasis exacerbations over a 52-week treatment period compared with placebo. ASPEN further represents an opportunity to describe patient characteristics and variation in treatment practices in a unique global bronchiectasis cohort. Here, we outline the clinical trial design and describe the baseline characteristics of adult patients enrolled in the ASPEN trial. Full trial results will be reported in a future publication.

Methods

Study design and end-points

ASPEN is an ongoing, phase 3, randomised, double-blind, placebo-controlled global study designed to assess the efficacy, safety and tolerability of brensocatib *versus* placebo in patients with bronchiectasis and ⩾2 exacerbations in the past 12 months. Patients were randomised 1:1:1 to receive brensocatib (10 mg or 25 mg) once daily or matching placebo for 52 weeks, followed by 1 month off treatment (figure 1). Assessments occurred during both in-clinic visits (baseline; weeks 4, 16, 28, 40 and 52; and end of study at week 56) and telephone visits (weeks 10, 22, 34 and 46).

The primary end-point of the study is the annualised rate of exacerbations over the 52-week treatment period, comparing both brensocatib doses to placebo. Exacerbations were defined using the EMBARC/Bronchiectasis and nontuberculous mycobacterial (NTM) Research Registry (BRR) definition as having ⩾3 of the following symptoms for at least 48 h, resulting in a physician's decision to prescribe systemic antibiotics: 1) increased cough; 2) increased sputum volume or change in sputum consistency; 3) increased sputum purulence; 4) increased breathlessness and/or decreased exercise tolerance; 5) fatigue and/or malaise; and 6) haemoptysis [20].

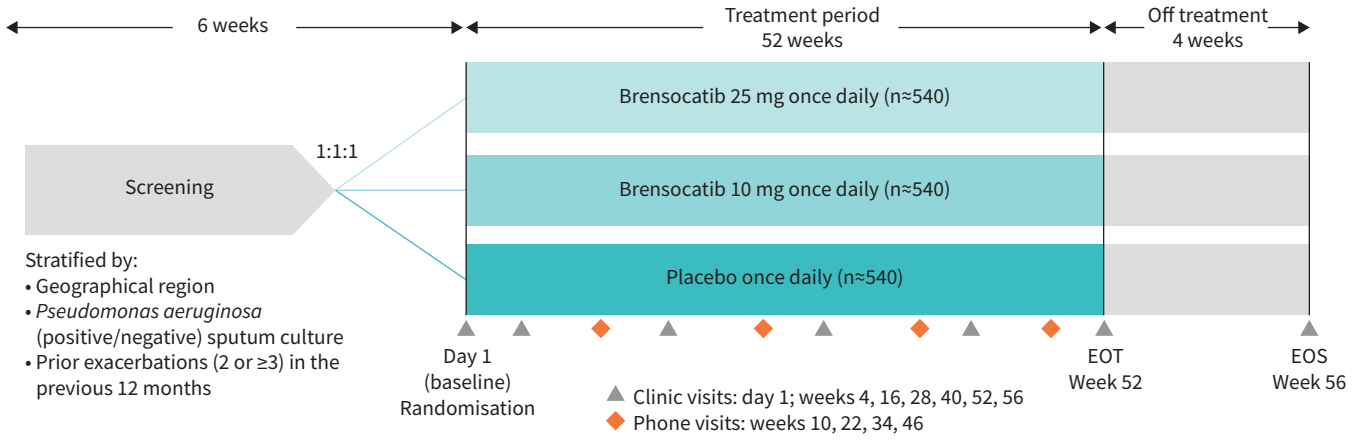

FIGURE 1 Study design. EOS: end of study; EOT: end of treatment.

Secondary end-points include time to first bronchiectasis exacerbation, proportion of patients remaining exacerbation free, frequency of severe exacerbations (requiring intravenous antibacterial drug treatment and/or hospitalisation), change from baseline to week 52 in post-bronchodilator forced expiratory volume in 1 s (FEV_1), change from baseline to week 52 in the Quality of Life Questionnaire-Bronchiectasis (QoL-B) Respiratory Symptoms domain score, safety and brensocatib pharmacokinetics.

Participants

Key inclusion criteria

Eligible patients were 18 to 85 years old with a body mass index ⩾18.5 $kg \cdot m^{-2}$ at baseline and a clinical history consistent with bronchiectasis (cough, chronic sputum production and/or recurrent respiratory infections), confirmed by radiologist examination of computerised tomography (CT) of the chest demonstrating bronchiectasis affecting ⩾1 lobe. Patients were required to have had ⩾2 exacerbations in the previous 12 months, defined by the need for antibiotic prescription.

The study was done in accordance with the Declaration of Helsinki and approved by the institutional review board and ethics committees at individual study sites.

Key exclusion criteria

Patients with comorbid asthma or COPD were excluded if the investigator determined that respiratory symptoms were driven primarily by the COPD or asthma comorbidities rather than by bronchiectasis. Medications with the potential to impact the inflammatory response or immune function were prohibited to avoid serious infections induced by immune suppression (*e.g.*, chronic systemic steroids at any dose or use of immunomodulatory agents). Patients were excluded if they were known to have cystic fibrosis, were receiving supplemental oxygen >12 h per day, were current smokers or were currently being treated for allergic bronchopulmonary aspergillosis, tuberculosis or NTM lung disease (a prior history of NTM lung infection was not an exclusion criterion).

Randomisation

Patients were randomised in a 1:1:1 ratio to receive an oral dose of brensocatib 10 mg, brensocatib 25 mg or placebo once daily, using a central Interactive Web Response System. Randomisation was stratified according to region (North America, Europe, Japan and the rest of the world), *Pseudomonas aeruginosa* culture status at screening (positive or negative) and the number of bronchiectasis exacerbations in the 12 months prior to screening (2 or ⩾3).

Analyses and assessments at screening and baseline

At screening, patient demographics, medical history, exacerbation history and prior and concomitant medications were recorded. Sputum was sent for central laboratory culture to identify patients with *P. aeruginosa* (for the purpose of stratification), and patients performed lung function spirometry (pre- and post-bronchodilator FEV_1 and % predicted FEV_1 ($ppFEV_1$), forced vital capacity (FVC), forced expiratory flow between 25% and 75% of vital capacity and peak expiratory flow rate) [21]. In view of the recent

description of an eosinophilic bronchiectasis endotype, patients were assessed for blood eosinophil levels and classified as eosinophilic at counts ⩾300 cells·μL^{-1} [22].

Baseline assessments included the Bronchiectasis Severity Index (BSI) [23] and QoL using the QoL-B Respiratory Symptoms domain score (range, 0–100). During the trial, symptom burden was assessed using the Bronchiectasis Exacerbation and Symptom Tool (BEST; range, 0–26), which patients performed on a daily basis during the study [24]. Increasing BEST scores were used to alert sites to possible deteriorations in symptoms and to review whether patients were experiencing pulmonary exacerbations. The most recent chest CT scan (not older than 5 years before the screening date) was selected to calculate the Bronchiectasis-Computed Tomography (BE-CT) score (range 1–18) and assess the severity of disease in each patient.

Region definitions

Regions were defined as follows, to be consistent with the randomisation stratification of the study (geographic regions (North America, Europe, Japan, Rest of World): Western Europe (Austria, Belgium, Denmark, France, Germany, Greece, Ireland, Italy, the Netherlands, Portugal, Spain, UK, Turkey, Israel); Latin America (Argentina, Brazil, Chile, Colombia, Mexico, Peru); North America (US, Canada); Eastern Europe (Bulgaria, Hungary, Latvia, Poland, Serbia, Slovakia); Australia/New Zealand (Australia, New Zealand); Southeast Asia (Taiwan, Thailand, Malaysia, South Korea); and Japan. Greece, Israel, Italy, Portugal, Spain and Turkey were classified within the Western Europe region due to similar patient characteristics.

Sample size and statistical analysis

Inclusion of 1620 adult patients yielded 90% power to detect a 30% reduction in the exacerbation rate ratio with an overall α level of 0.01 between any of the brensocatib treatment arms and placebo after 52 weeks of treatment. The α level of 0.01 was chosen in alignment with the US Food and Drug Administration, and with the Committee for Medicinal Products for Human Use of the European Medicines Agency reflective of a single large trial being used for registrational purposes.

Descriptive statistics were used to describe the frequency of different characteristics between groups at baseline. At the time of writing, the study remains blinded; therefore, all data are presented with the three study groups combined.

Subgroup analyses of the primary end-point will be performed on important demographic and clinical variables, such as *P. aeruginosa* culture status, long-term antibiotic use (such as macrolides, inhaled antibiotics and non-macrolide systemic antibiotics), prior history of exacerbations (2 or ⩾3), BSI and blood eosinophil count (<300 or ⩾300 cells·μL^{-1}).

All statistical analyses were done with Statistical Analysis System (SAS) software for Windows, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient recruitment and baseline characteristics

Recruitment into the ASPEN trial began in December 2020 and was completed in March 2023. A total of 1682 adults were randomised at 359 clinical sites in 35 countries. Patient enrolment per region is shown in supplementary figure S1. No single country contributed >15% of the total study population. Regional enrolment was as follows: Western Europe (482; 28.7%); Latin America (473; 28.1%); North America (249; 14.8%); Eastern Europe (169; 10.0%); Australia/New Zealand (133; 7.9%); Southeast Asia (89; 5.3%); and Japan (87; 5.2%).

The baseline characteristics of enrolled patients are shown in table 1. The mean age of patients was 61.3 years, 64.7% were female and 73.4% were white. ∼70% of patients had moderate-to-severe BSI scores, 29.3% had ⩾3 exacerbations in the prior 12 months and 35.7% were positive for *P. aeruginosa* at baseline. 18.4% of patients had eosinophil levels ⩾300 cells·μL^{-1}.

Severity of disease

Mean±SD BSI scores were highest in Australia and New Zealand (8.3±3.9), followed by Japan (8.2±4.1), North America (8.0±3.6), Southeast Asia (7.6±3.3), Western Europe (7.3±3.6), Eastern Europe (7.2±3.1) and Latin America (5.9±3.1) (figure 2). Notably, all regions except Latin America had at least one-third of patients with BSI scores reflecting severe disease.

TABLE 1 Patient demographics and characteristics

	ASPEN cohort[#]
Age years, mean±SD	61.3±14.2
⩾65 years, n (%)	841 (50.0)
⩾75 years, n (%)	262 (15.6)
Sex, n (%)	
Female	1088 (64.7)
Race, n (%)	
White	1235 (73.4)
Black or African American	10 (0.6)
Asian	189 (11.2)
American Indian or Alaska Native	23 (1.4)
Native Hawaiian or Pacific Islander	2 (0.1)
>1 race	37 (2.2)
Not reported/unknown/other	186 (11.1)
BMI kg·m^{-2}, mean±SD	25.5±5.1
Smoking status/ever smoked, n (%)	
Never	1169 (69.5)
Ex-smoker	513 (30.5)
Pack-years smoked in ex-smokers, mean±SD	16.3±20.5
MRC dyspnoea score, n (%)	
1–3	1604 (95.4)
4	66 (3.9)
5	12 (0.7)
***Pseudomonas aeruginosa*, n (%)**	
Positive	600 (35.7)
Exacerbations in prior 12 months, n (%)	
2	1190 (70.7)
3 or more	492 (29.3)
BSI, mean±SD	7.1±3.6
Overall BSI score categories, n (%)	
⩽4	435 (25.9)
5–8	714 (42.4)
⩾9	533 (31.7)
Eosinophil count (average cells·mm^{-3}), mean±SD	218.5±234.0
Blood eosinophil, n (%)	
<300 cells·µL^{-1}	1232 (73.2)
⩾300 cells·µL^{-1}	309 (18.4)
Missing	141 (8.4)
QoL-B RSS, median (IQR)	63.0 (25.9)

All data are Visit 2 (Baseline) data except where indicated. BMI: body mass index; MRC: Medical Research Council; BSI: Bronchiectasis Severity Index; QoL-B RSS: Quality of Life Questionnaire-Bronchiectasis Respiratory Symptom scores. [#]: n=1682.

The mean±SD post-bronchodilator ppFEV$_1$ was 73.2±23.4%, with 37.7% of patients having ppFEV$_1$ >80% and 17.6% of patients having ppFEV$_1$ <50% (table 2). Patients with FEV$_1$ >80% predicted and FEV$_1$/FVC ratio >0.7 represented 30.6% of the total.

Aetiology and comorbidity

The most common bronchiectasis aetiology was idiopathic in 982 (58.4%) patients, followed by post-infective (pneumonia/childhood infections) in 496 (29.5%) and primary ciliary dyskinesia in 111 (6.6%) (figure 3). Idiopathic aetiology was most common in Southeast Asia (n=70; 78.7%), Japan (n=68; 78.2%) and North America (n=161; 64.7%). Patients from Eastern Europe had the lowest proportion with idiopathic aetiology (n=71; 42.0%).

Respiratory and non-respiratory comorbidities are shown in figure 4. Respiratory comorbidities included COPD (14.8%) and asthma (18.1%). The highest rates of comorbid COPD were reported in Southeast Asia (37.1%) and Eastern Europe (34.9%), whereas the highest rates of comorbid asthma were reported in Australia and New Zealand (37.6%) (figure 4b).

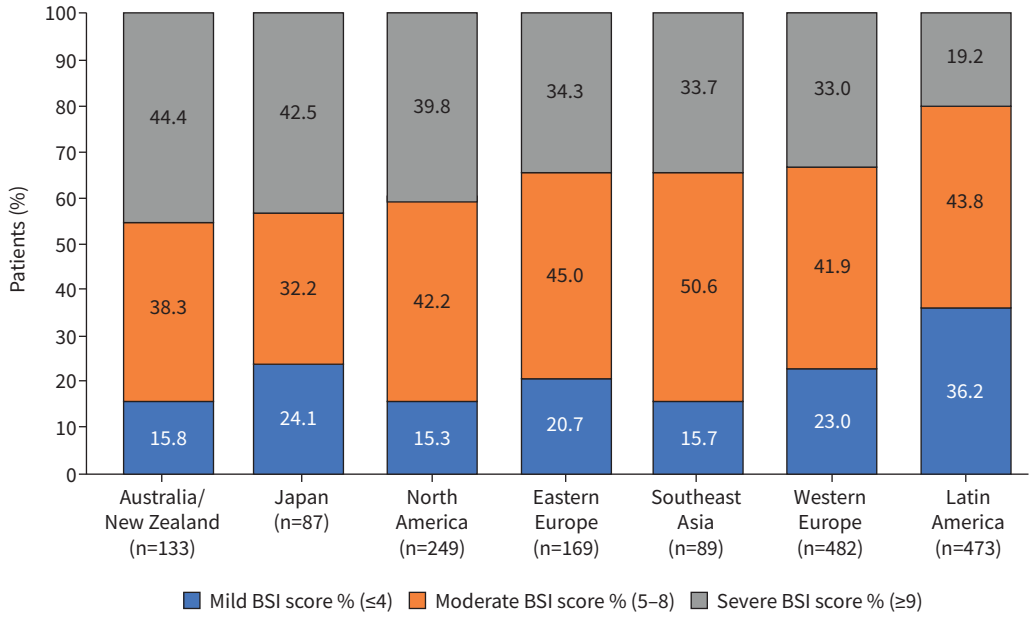

FIGURE 2 Severity of bronchiectasis in the 12 months prior to baseline across regions. Proportion of patients with mild (BSI ⩽4), moderate (BSI 5–8) or severe (BSI ⩾9) BSI scores across regions. Regions are ordered by the proportion of patients with severe bronchiectasis according to BSI score, from highest on the left. BSI: Bronchiectasis Severity Index.

Treatments

At baseline, concomitant medications included inhaled corticosteroids (ICS) in 57.3% of patients (table 3), long-acting β2-agonists (LABA) in 50.4%, long-acting muscarinic antagonists (LAMA) in 16.5%, and carbocisteine or N-acetylcysteine in 6.5%. Oral macrolides were the most commonly used long-term antibiotics (16.6% of patients), followed by inhaled antibiotics (5.8%) and other oral antibiotics (3.5%).

Geographical variation in concomitant medications was observed. Use of ICS was highest in Latin America (68.3%) and Australia/New Zealand (63.2%), with lowest use observed in Japan (20.7%). Use of long-term antibiotics also varied widely, with the highest macrolide use in Japan (75.9%) followed by

TABLE 2 Lung function

Parameter	ASPEN cohort[#]
Lung function, mean±SD	
Post-BD FEV_1 L	1.93±0.78
Post-BD FEV_1 % predicted	73.2±23.4
Post-BD FVC L	2.82±0.99
Post-BD FVC % predicted	81.6±19.3
Post-BD % predicted FEV_1 categories, n (%)	
>80%	634 (37.7)
50–80%	728 (43.3)
30–49%	287 (17.1)
<30%	9 (0.5)
Lung function pattern post-BD spirometry, n (%)	
Obstruction (FEV_1/FVC <0.7)	842 (50.1)
PRISm[¶]	301 (17.9)
Normal spirometry (FEV_1 >80% predicted and FEV_1/FVC >0.7)	515 (30.6)

BD: bronchodilator; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; PRISm: preserved ratio impaired spirometry. [#]: n=1682; [¶]: PRISm, FEV_1 <80% of predicted and FEV_1/FVC ratio >0.7 [19].

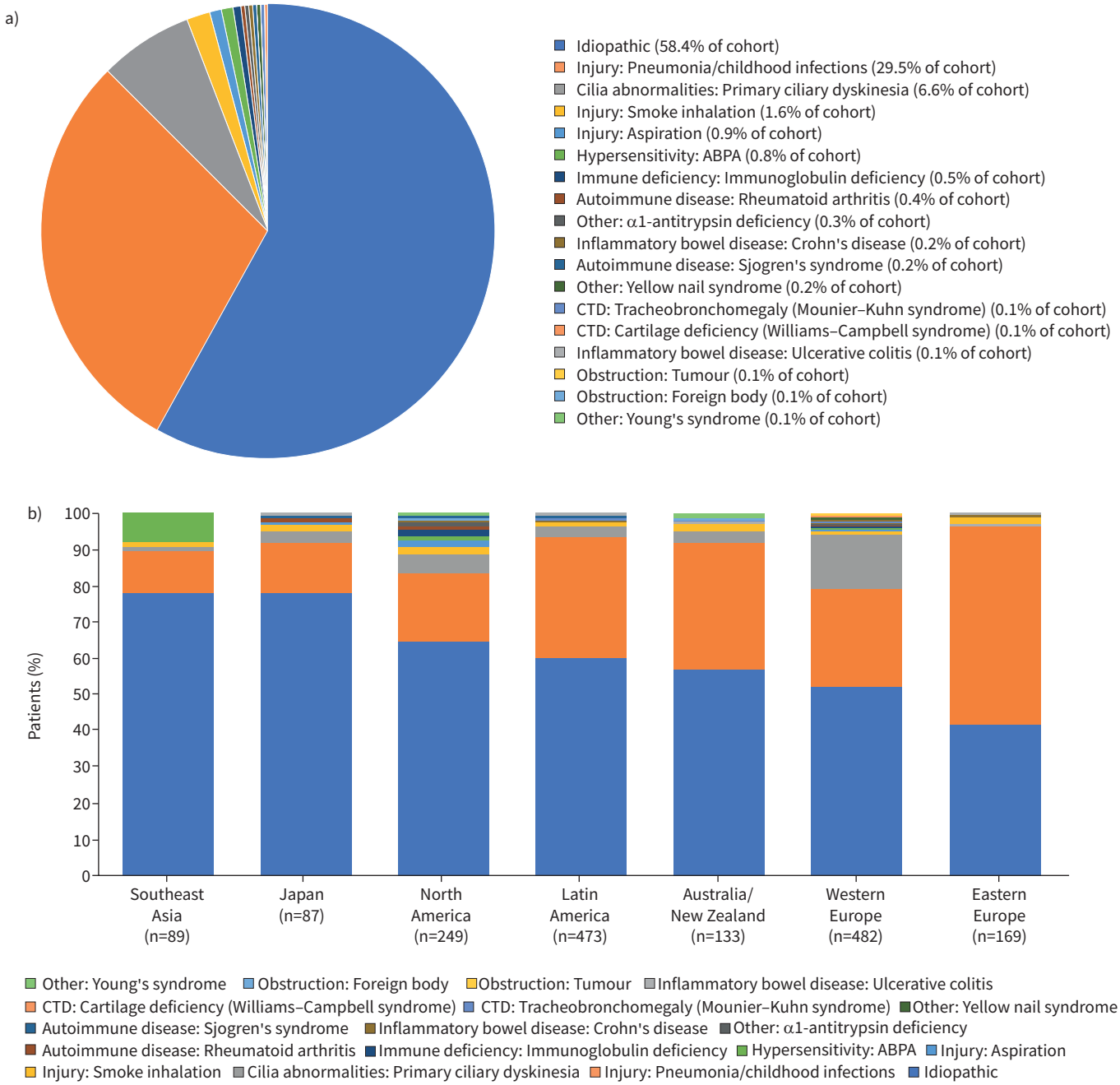

FIGURE 3 Aetiologies of bronchiectasis provided as overall and by region. a) Aetiologies of bronchiectasis provided for the ASPEN cohort. b) Aetiologies of bronchiectasis provided by region. Regions are ordered by idiopathic aetiology, from highest on the left.

Australia/New Zealand (23.3%) and Western Europe (19.9%) (table 3). There was also higher use of mucoactive drugs, such as oral N-acetylcysteine and carbocisteine, in Japan and Southeast Asia compared with other regions.

Pseudomonas aeruginosa

All patients had sputum tested for *P. aeruginosa* at screening. Positive *P. aeruginosa* culture at screening varied by region, with the highest percent of positive patients in Southeast Asia (n=48, 53.9%), followed by Japan (n=41, 47.1%), North America (n=102, 41.0%), Latin America (n=177, 37.4%), Australia/New Zealand (n=46, 34.6%), Western Europe (n=147, 30.5%), and the lowest in Eastern Europe (n=39, 23.1%). Overall, age and exacerbation history were similar between patients who were *P. aeruginosa*-positive

a)

Comorbidity	ASPEN cohort (n=1682)
Respiratory comorbidities	
Asthma	304 (18.1)
COPD	249 (14.8)
Non-respiratory comorbidities	
Cardiovascular	251 (14.9)
Osteoporosis	163 (9.7)
Diabetes	162 (9.6)
Depression	125 (7.4)
Anxiety	98 (5.8)
Neoplasm	69 (4.1)
Chronic renal failure	21 (1.2)
Stroke	2 (0.1)
Liver disease	1 (0.1)

b)

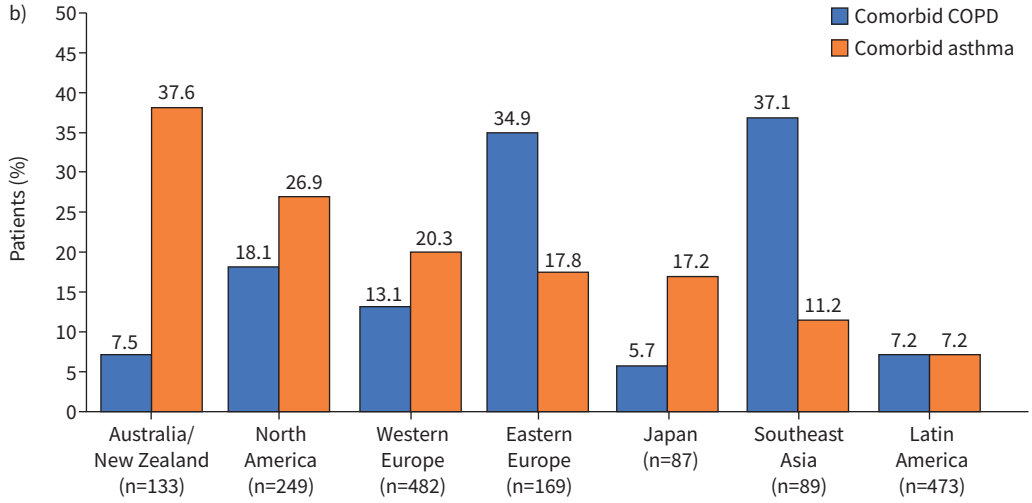

FIGURE 4 Respiratory and non-respiratory comorbidities in the full ASPEN cohort and respiratory comorbidities by region. a) Respiratory and non-respiratory comorbidities in the full ASPEN cohort. Data are presented as n (%). b) Respiratory comorbidities by region. Regions are ordered by comorbid asthma, from highest on the left.

versus P. aeruginosa-negative at baseline. A higher proportion of *P. aeruginosa*-positive patients were women (70.0% *versus* 61.7%). Lung function was lower among *P. aeruginosa*-positive patients (mean±SD post-bronchodilator ppFEV$_1$ 64.7±21.0% *versus* 77.9±23.4%). Patients with *versus* without *P. aeruginosa* received more long-term antibiotics with greater overall long-term macrolide use (21.5% *versus* 14.0%), and more frequent use of ICS (63.5% *versus* 53.9%). There was also a wide regional variation in the use of long-term antibiotics in patients with *P. aeruginosa*, with no use in Eastern Europe, high use in Japan, and similar use in Western Europe and North America (figure 5b).

Discussion

We report the study design and the characteristics of adult patients in ASPEN, a phase 3 trial of brensocatib, the largest bronchiectasis global clinical programme to date, with 1682 patients, spanning 35 countries and five continents. The patient population, with a mean age of 61 years, included 64.7% women, most with idiopathic aetiology, and the most common respiratory comorbidities as a secondary diagnosis were asthma and COPD.

The study participants displayed several features typical of the broader population of patients with bronchiectasis. For example, in an analysis of the EMBARC Registry of 16 963 patients from 28 countries in Europe, the median age was 67 years and 60.9% of participants were women [7]. Data from the BRR showed the majority (79%) of patients with bronchiectasis were women and had a mean age of 64 years [9]. Emerging evidence suggests an eosinophilic endotype among patients with bronchiectasis, supporting the

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TABLE 3 Concomitant medications and long-term antibiotic use by region

Concomitant medications	ASPEN cohort	Australia/New Zealand	Eastern Europe	Western Europe	Japan	Latin America	North America	Southeast Asia
Patients, n	1682	133	169	482	87	473	249	89
Inhaled steroids	964 (57.3)	84 (63.2)	61 (36.1)	279 (57.9)	18 (20.7)	323 (68.3)	154 (61.8)	45 (50.6)
LABA	847 (50.4)	69 (51.9)	51 (30.2)	238 (49.4)	16 (18.4)	312 (66.0)	114 (45.8)	47 (52.8)
LAMA	278 (16.5)	20 (15.0)	16 (9.5)	77 (16.0)	7 (8.0)	84 (17.8)	38 (15.3)	36 (40.4)
Mucoactive drugs								
Carbocisteine or N-acetylcysteine	110 (6.5)	0	0	34 (7.1)	37 (42.5)	14 (3.0)	1 (0.4)	24 (27.0)
Hypertonic saline	38 (2.3)	10 (7.5)	0	16 (3.3)	0	1 (0.2)	11 (4.4)	0
Ambroxol hydrochloride	33 (2.0)	0	2 (1.2)	0	24 (27.6)	0	0	7 (7.9)
Bromhexine hydrochloride	8 (0.5)	6 (4.5)	0	1 (0.2)	1 (1.1)	0	0	0
DNAse	6 (0.4)	1 (0.8)	0	2 (0.4)	0	0	3 (1.2)	0
Isotonic saline	6 (0.4)	0	0	6 (1.2)	0	0	0	0
Long-term antibiotics								
Oral macrolides	280 (16.6)	31 (23.3)	0	96 (19.9)	66 (75.9)	52 (11.0)	30 (12.0)	5 (5.6)
Inhaled antibiotics	97 (5.8)	3 (2.3)	0	56 (11.6)	0	7 (1.5)	30 (12.0)	1 (1.1)
Other oral antibiotics	59 (3.5)	9 (6.8)	0	17 (3.5)	1 (1.1)	6 (1.3)	24 (9.6)	2 (2.2)

Data are presented as n (%) unless indicated otherwise. LABA: long-acting β2-agonist; LAMA: long-acting muscarinic antagonist.

a)

	Pseudomonas aeruginosa-positive at baseline (n=600)	*Pseudomonas aeruginosa*-negative at baseline (n=1082)
Age years, mean±SD	61.3 (14.57)	61.3 (13.99)
Sex, female, n (%)	420 (70.0)	668 (61.7)
Number of exacerbations in prior 12 months, n (%)		
2	418 (69.7)	772 (71.3)
≥3	182 (30.3)	310 (28.7)
Post-BD FEV_1 L, mean±SD	1.65 (0.678)	2.09 (0.789)
Post-BD FEV_1 % predicted, mean±SD	64.7 (20.99)	77.9 (23.40)
Eosinophil count (cells·mm^{-3}), mean±SD	211.7 (178.1)	222.3 (260.1)
Blood eosinophil, n (%)		
<300 cells·µL^{-1}	448 (74.7)	784 (72.5)
≥300 cells·µL^{-1}	106 (17.7)	203 (18.8)
Missing	46 (7.7)	95 (8.8)
Long-term antibiotic use, n (%)	187 (31.2)	200 (18.5)
Macrolides	129 (21.5)	151 (14.0)
Inhaled antibiotics	57 (9.5)	40 (3.7)
Other oral antibiotics	25 (4.2)	34 (3.1)
Use of ICS, n (%)	381 (63.5)	583 (53.9)

b)

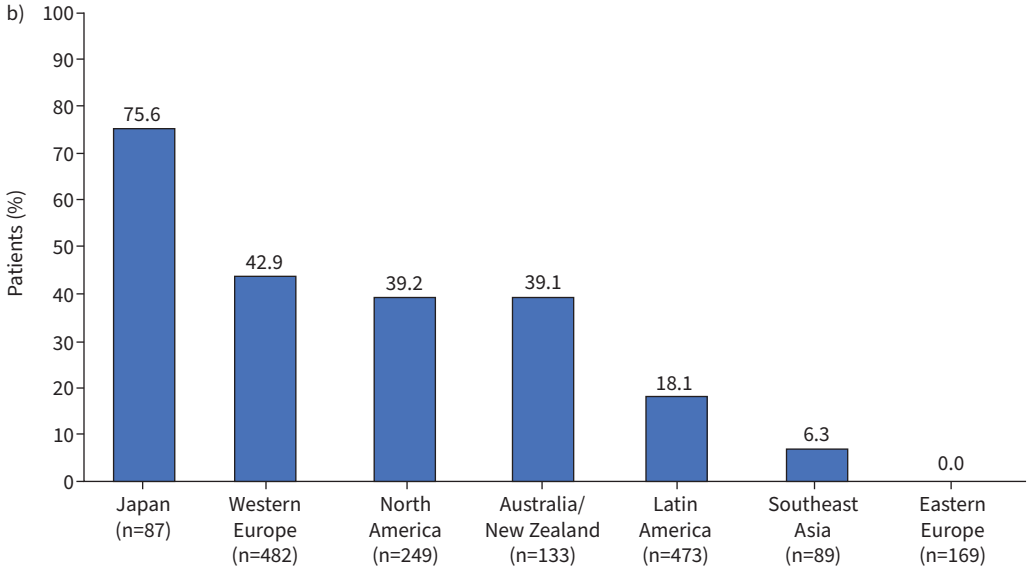

FIGURE 5 Demographics, characteristics, and long-term antibiotic use stratified by *Pseudomonas aeruginosa* positivity at baseline. a) Demographics and characteristics of patients with a positive sputum culture for *P. aeruginosa* at baseline. b) Long-term antibiotic use in patients with a positive sputum culture for *P. aeruginosa* at baseline. Regions are ordered by long-term use, from highest on the left. BD: bronchodilator; FEV_1: forced expiratory volume in 1 s; ICS: inhaled corticosteroids.

rationale to collect blood eosinophil counts in ASPEN. The proportion of patients with peripheral blood eosinophil counts at baseline ⩾300 cells·µL^{-1} was 18.4%, similar to what has been previously reported [22].

P. aeruginosa is one of the most common pathogens in bronchiectasis [25]. A unique feature of the ASPEN study design is that all participants had a sputum sample sent for *P. aeruginosa* culture at screening, representing the largest ever systematic global screening for *P. aeruginosa* in this disease. Notably, the proportion of patients with a sputum sample positive for *P. aeruginosa* was similar to previous findings [9]. Patients with *P. aeruginosa* infection are known to have a higher burden of disease [23]. In ASPEN, 35.2% of patients with positive *P. aeruginosa* sputum samples at screening received long-term antibiotics; however, there was geographical variation in long-term macrolide use, with the highest rates observed in Japan.

The most common aetiologies of bronchiectasis in ASPEN were idiopathic, pneumonia/childhood infections and cilia abnormalities/primary ciliary dyskinesia, which contributed to over 90% of cases. Aetiologies varied by region, with the lowest proportion of idiopathic aetiology in Eastern Europe (42.0%) and the largest in Southeast Asia (79.8%). These observations were very similar to what has been reported out of the EMBARC registry, where the most common aetiology was idiopathic (38.1%), followed by post-infective disease (21.2%) [7]. The larger percentage of patients with idiopathic aetiology in ASPEN compared with EMBARC may reflect the inclusion of non-European regions in ASPEN. Finally, the fact that primary ciliary dyskinesia was the third most common aetiology identified in ASPEN, an aetiology that has been associated with more severe bronchiectasis [26], and was more frequent than has been reported in large adult registry studies suggests that these patients may be likely to have a severe bronchiectasis phenotype. Notably, primary ciliary dyskinesia was quite variable among regions, which may be due to differences in gene carriage prevalence or differences in testing availability in different regions.

The most commonly reported respiratory comorbidities as a secondary diagnosis were asthma (18.1%) and COPD (14.8%), which often overlap with bronchiectasis and are associated with worse clinical outcomes [27].

Australia/New Zealand had the highest percentage of patients with asthma (37.6%), compared with Southeast Asia (11.2%) and Latin America (7.2%). Southeast Asia (37.1%) and Eastern Europe (34.9%) had the highest frequency of patients with COPD, possibly driven by higher rates of smoking in those regions [28]; whereas Latin America (7.2%) and Japan (5.7%) had the lowest frequency of COPD. The inverse relationship between COPD and asthma diagnosis may point to this merely being different patterns of use of these terms in different regions, as these terms are physician assigned and not necessarily confirmed.

Results from a systematic review and meta-analysis demonstrated a 36.6% mean prevalence of bronchiectasis among patients with asthma, with these patients having lower FEV_1/FVC and more frequent exacerbations than patients with asthma alone [29]. Comorbid bronchiectasis in COPD has also been associated with increased exacerbation, severe airway obstruction and mortality [30]. Consequently, smoking has been associated with bronchiectasis in young adults, with stronger associations in women, persons aged 20 to 29 years, and the overweight and obese population [31].

BSI, a score that predicts 1- and 4-year morbidity and mortality for patients with bronchiectasis [23], varied per region, with Australia/New Zealand (44.4%) and Japan (42.5%) having the largest proportion of patients with severe disease and Latin America (19.2%) having the lowest proportion of patients with severe disease. However, BSI is designed to look at future mortality risk, and while patients may be classified as having mild, moderate or severe BSI scores, the reality of their disease may be more complex. For example, a patient with a lower BSI score who is experiencing frequent exacerbations would not be considered as having “mild disease” in clinical practice.

Exacerbation frequency is associated with increased disease severity, poor health-related QoL and increased all-cause mortality [6]. Despite partial enrolment during the COVID-19 pandemic and the associated evolution of social distancing and lockdown procedures to the relaxation of these public health measures, the proportion of patients with $\geqslant$3 exacerbations in the prior 12 months was very similar to previous findings in the phase 2 WILLOW study, which was completed prior to the pandemic, and other published observations [19].

The most common concomitant medication in this study was ICS (57.3%), followed by LABA (50.4%). This is much higher than the proportion of participants reporting asthma and COPD comorbidities and therefore reflects overuse as guidelines recommend not to use ICS in patients with bronchiectasis in the absence of comorbid asthma or COPD. 25.9% of the patient population were taking long-term antibiotics and, similar to the data presented in the EMBARC study, the most common antibiotics used were macrolides (16.6%) [7]. Overall, the geographical heterogeneity of treatment regimens likely reflects variation in resources and lack of high-quality evidence for specific treatments.

The current analysis is limited by the focus on baseline characteristics of the trial population. Additional analyses are needed to investigate eosinophil count, asthma and FEV_1 bronchodilator responsiveness. Notably, there is an expanded access study that allows early brensocatib treatment for patients following the ASPEN trial.

In the phase 2 WILLOW trial, treatment with brensocatib *versus* placebo prolonged the time to first exacerbation, and reduced sputum NE activity, in 256 adult patients with bronchiectasis, demonstrating the potential clinical benefits of DPP-1 inhibition in the management of bronchiectasis [19]. ASPEN is the

largest clinical trial programme in bronchiectasis to date, enrolling over 1600 patients in 35 countries. While individual registries have reported data from Europe, USA, India, Korea, Australia and other countries, ASPEN is the first study with a large sample size to provide comparative data on demographics, severity, microbiology and treatment patterns across different continents. Baseline data reported here were broadly representative of a global subset of patients with bronchiectasis. The diversity of exposures and clinical management across the globe is expected to be balanced between study arms through stratification and randomisation by region, *P. aeruginosa* culture status and number of bronchiectasis exacerbations in the prior 12 months. Future publications will report on efficacy, safety and tolerability of brensocatib in people with bronchiectasis.

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This study is registered at www.clinicaltrials.gov with identifier number NCT04594369 and https://eudract.ema.europa.eu/ with identifier number 2020-003688-25.

Ethics statement: The study was performed in accordance with the Declaration of Helsinki, and approved by the institutional review boards and ethics committees at individual study sites.

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