# Brensocatib in patients with bronchiectasis: subgroup analyses from the WILLOW trial

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***Post hoc* analyses from the WILLOW trial found that brensocatib showed efficacy in subgroups of patients with bronchiectasis defined by key baseline disease characteristics (BSI, blood eosinophil count, exacerbation frequency, macrolide use, *P. aeruginosa*)** https://bit.ly/4bZX7Hy

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## Abstract

***Introduction*** Bronchiectasis is a chronic inflammatory airway disease. Brensocatib, an oral, reversible inhibitor of dipeptidyl peptidase 1 (DPP1), reduces pulmonary inflammation by preventing the activation of neutrophil serine proteases. In the phase II WILLOW trial, brensocatib prolonged time to first exacerbation in patients with bronchiectasis. In this *post hoc* analysis we compare clinical outcomes in patients from WILLOW according to baseline disease characteristics.

***Methods*** Adults with bronchiectasis treated with brensocatib (10 or 25 mg) or placebo once daily were analysed by baseline Bronchiectasis Severity Index (BSI) score (⩽4 (mild), 5–8 (moderate), or ⩾9 (severe)), exacerbation history (2 or ⩾3 in the previous year), blood eosinophil count (<300 cells per µL or ⩾300 cells per µL), long-term macrolide use (⩾6 months; no or yes) and *Pseudomonas aeruginosa* culture at screening (negative or positive). End-points were time to first exacerbation, annualised exacerbation rate, change in lung function from baseline, and safety. All patients who received brensocatib were pooled and compared with placebo.

***Results*** Treatment with brensocatib *versus* placebo was associated with a longer time to first exacerbation (hazard ratio (95% confidence interval), BSI: ⩽4, 0.28 (0.08–0.96); 5–8, 0.75 (0.35–1.60); ⩾9, 0.61 (0.35–1.04); prior exacerbations: 2, 0.56 (0.34–0.90); ⩾3, 0.71 (0.32–1.59); blood eosinophils per µL: <300, 0.66 (0.42–1.06); ⩾300, 0.49 (0.20–1.20); long-term macrolide use: no, 0.60 (0.38–0.94); yes, 0.60 (0.25–1.45); *P. aeruginosa* culture: negative, 0.54 (0.32–0.92); positive, 0.68 (0.37–1.27)). Safety results were similar across subgroups.

***Discussion*** Patients treated with brensocatib had a numerically longer time to first exacerbation and reduced annualised rate of exacerbation *versus* placebo across all key baseline disease characteristics.

## Introduction

Noncystic fibrosis (non-CF) bronchiectasis is a complex inflammatory disease characterised by permanent dilation of the bronchi with persistent cough, sputum production and periods of worsening symptoms or exacerbations [1, 2]. Exacerbations are associated with increased morbidity and all-cause mortality, as well as reduced lung function, worse quality of life and increased airway inflammation [3–5].

Inflammation in non-CF bronchiectasis is predominantly neutrophilic [6]. The neutrophil serine proteases (NSPs) neutrophil elastase (NE), cathepsin G and proteinase 3 are activated by dipeptidyl peptidase-1 (DPP1, also known as cathepsin C) during neutrophil maturation in the bone marrow. During pulmonary

inflammation, NSPs are released extracellularly, predominantly through the formation of neutrophil extracellular traps [6, 7]. Increased sputum NE activity is a marker for worse bronchiectasis disease severity, higher risk of exacerbation, decreased lung function and increased all-cause mortality [4]. Although neutrophils are the most abundant inflammatory cell in the airways of patients with bronchiectasis, eosinophilic inflammation has also been described in up to 30% of patients with non-CF bronchiectasis, though most patients show evidence of a "mixed" phenotype consisting of both neutrophilic and eosinophilic inflammation [8–11]. Regardless, the importance of inflammation in non-CF bronchiectasis is clear as increased levels of both neutrophilic and eosinophilic airway inflammation have been linked to an increased risk of exacerbations and disease severity in patients with non-CF bronchiectasis [4, 7, 9].

As a key driver of disease progression, neutrophilic inflammation may serve as a therapeutic target for patients with non-CF bronchiectasis [4, 7]. Brensocatib is an investigational once-daily, oral, reversible DPP1 inhibitor that prevents the activation of NSPs during neutrophil maturation in the bone marrow, including NE [12]. In the phase II, randomised, double-blind WILLOW trial (ClinicalTrials.gov identifier NCT03218917; EudraCT number: 2017-002533-32), patients with non-CF bronchiectasis treated with 10 or 25 mg once-daily brensocatib had a prolonged time to first exacerbation and a reduced rate of exacerbations compared with patients treated with placebo [12]. A larger proportion of patients treated with either dose of brensocatib also remained exacerbation free during the 24-week trial period and, on average, patients who received brensocatib treatment had lower reduction in lung capacity compared with placebo [12]. Nevertheless, given the heterogeneity of non-CF bronchiectasis [1], it is important to establish whether the efficacy of anti-inflammatory therapy varies by disease subgroup such as disease severity, chronic infection, frequency of exacerbations or inflammatory endotype. Additionally, macrolides reduce exacerbations in patients with non-CF bronchiectasis, an effect which may be mediated through reduced neutrophilic inflammation [13, 14]. It is therefore also important to understand if additive benefits can be demonstrated for DPP1 inhibition on top of long-term macrolide treatment.

Previous subgroup analyses of the time to first exacerbation from the WILLOW trial indicated a trend toward benefit for patients treated with either dose of brensocatib in all subgroups investigated including age, exacerbation frequency and baseline indicators of disease severity [12]. In the *post hoc* analyses presented here, we expanded upon these previous analyses to evaluate whether the efficacy of brensocatib in the pooled brensocatib treatment groups was consistent across patient subgroups from the WILLOW trial based on the disease characteristics, BSI score, exacerbation frequency, blood eosinophil counts, macrolide use and *Pseudomonas aeruginosa* infection status.

## Methods

### *Trial design and procedures*

Complete details of the WILLOW trial design have been previously reported in the primary publication [12]. WILLOW was a phase II, double-blind, placebo-controlled trial conducted at 116 sites across 14 countries. After a 6-week screening period, eligible adults (aged 18 to 85 years) with non-CF bronchiectasis who had experienced at least two exacerbations in the previous year were randomised 1:1:1 to receive brensocatib 10 mg, brensocatib 25 mg or placebo once daily for 24 weeks. All patients provided written informed consent before participation. The study was conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki, with protocol approval from local institutional review boards and independent ethics committees.

### *End-points and assessments*

Efficacy assessments were conducted throughout the 24-week treatment period. Efficacy end-points included time to first exacerbation (primary end-point), annualised rate of exacerbations, and change from baseline in post-bronchodilator forced expiratory volume in 1 s ($FEV_1$). Exacerbations were defined as the presence of at least three of the following symptoms for at least 48 h 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 haemoptysis [15]. Safety end-points included treatment-emergent adverse events (TEAEs), adverse events of special interest (hyperkeratosis, periodontitis/gingivitis, and other infections), clinical laboratory assessment, vital signs and physical examination results; these were assessed from enrolment through week 28 in the safety population.

### *Statistical analysis*

Statistical methods mirrored those used in the primary WILLOW trial publication [12]. Analyses for efficacy end-points were performed based on the intention-to-treat population of all patients who were randomised to either dose of brensocatib or placebo. Time to the first exacerbation was analysed using a

Kaplan–Meier estimate and a stratified log-rank test, and annualised rate of exacerbations was analysed using a negative binomial model with a log-transformed time at risk as an offset variable and adjusted for covariates (treatment group, baseline *P. aeruginosa* status, and macrolide use). Change from baseline in $FEV_1$ was based on a restricted maximum likelihood based mixed model for repeated-measures approach and adjusted for covariates (treatment group, baseline *P. aeruginosa* status, macrolide use and baseline $FEV_1$ value). Summary statistics of safety end-points were based on the safety population of patients who received at least one dose of study drug (brensocatib or placebo). Patients who received either dose of brensocatib were pooled and compared descriptively with those who received placebo.

### *Subgroup analyses*

*Post hoc* subgroup analyses evaluated patients based on the following categorisations: 1) disease severity at baseline (BSI score of ⩽4 (mild) or 5–8 (moderate) or ⩾9 (severe)); 2) exacerbation frequency (2 or ⩾3 exacerbations in the year prior to enrolment); 3) blood eosinophil count at baseline (<300 cells per µL or ⩾300 cells per µL) [9]; 4) long-term macrolide use (⩾6 months before screening visit; yes or no); and 5) *P. aeruginosa* culture at screening (negative or positive). Due the *post hoc* nature of the findings, efficacy results are presented using treatment effect estimates with 95% confidence interval (CI) without p-values.

## Results

### *Patients*

In total, 256 patients were randomised into the WILLOW trial and included in the intention-to-treat population, with 87 patients assigned to the placebo group, 82 to the brensocatib 10 mg group and 87 to the brensocatib 25 mg group [12]. One patient assigned to the placebo group withdrew from the study prior to receiving study treatment and was excluded from the safety population (n=255). Baseline characteristics are shown in figure 1 and tables 1 and 2; specifics for each subgroup are detailed below.

At baseline, the mean (SD) BSI score in all patients was 8.3 (4.4). Of the 256 patients in the study, 53 (20.7%) had a BSI score of ⩽4 (mild), 89 (34.8%) had a BSI score of 5–8 (moderate), and 114 (44.5%) had a BSI score of ⩾9 (severe). Treatment groups were mostly balanced in baseline characteristics (table 1). For patients with a BSI score of ⩽4, variation between treatment groups was observed in sputum NE levels, long-term macrolide use, history of COPD or asthma and patient-reported outcome (PRO) measures. Treatment groups for patients with a BSI score of 5–8 also had variation in sputum NE levels, history of COPD or asthma and PROs, as well as sex and race. For patients with a BSI score of ⩾9, variation between treatment groups was observed in $FEV_1$ and use of inhaled antibiotics.

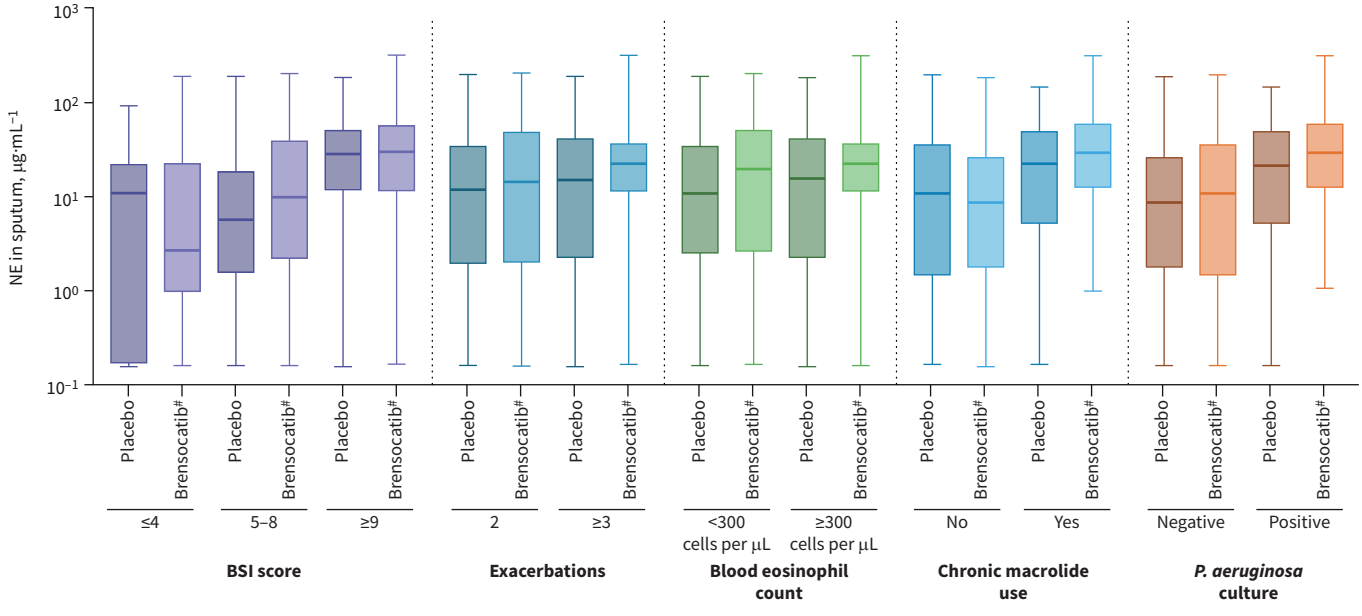


FIGURE 1 Baseline sputum neutrophil elastase (NE) levels across subgroups. Box and whisker plot represents the median, interquartile range, minimum and maximum values. BSI: Bronchiectasis Severity Index; *P. aeruginosa*: *Pseudomonas aeruginosa*. #: pooled brensocatib 10 mg and 25 mg doses.

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**TABLE 1** Baseline characteristics in WILLOW patients by subgroup: Bronchiectasis Severity Index (BSI) and exacerbation subgroups

| Characteristic | BSI | | | | | | Exacerbations in 12 months prior to baseline[#] | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ⩽4 (mild) | | 5–8 (moderate) | | ⩾9 (severe) | | 2 | | ⩾3 | |
| | Placebo | Brensocatib[¶] | Placebo | Brensocatib[¶] | Placebo | Brensocatib[¶] | Placebo | Brensocatib[¶] | Placebo | Brensocatib[¶] |
| **Patients, n** | 17 | 36 | 36 | 53 | 34 | 80 | 61 | 110 | 25 | 59 |
| **Age, years** | 58 (32–73) | 62 (24–75) | 67 (31–79) | 67 (22–80) | 70 (36–84) | 71 (28–83) | 66.0 (32–79) | 66.0 (22–83) | 67.0 (31–84) | 67.0 (24–80) |
| **Female sex** | 12 (70.6) | 28 (77.8) | 20 (55.6) | 37 (69.8) | 23 (67.6) | 54 (67.5) | 37 (60.7) | 75 (68.2) | 18 (72.0) | 44 (74.6) |
| **White race**[+] | 14 (82.4) | 32 (88.9) | 28 (77.8) | 51 (96.2) | 29 (85.3) | 71 (88.8) | 51 (83.6) | 104 (94.5) | 19 (76.0) | 50 (84.7) |
| **Exacerbations in prior 12 months** | | | | | | | | | | |
| 2 | 17 (100) | 28 (77.8) | 22 (61.1) | 38 (71.7) | 22 (64.7) | 44 (55.0) | 61 (100) | 110 (100) | 0 | 0 |
| 3 or more | 0 | 8 (22.2) | 13 (36.1) | 15 (28.3) | 12 (35.3) | 36 (45.0) | 0 | 0 | 25 (100) | 59 (100) |
| **BSI score categories** | | | | | | | | | | |
| ⩽4 | 17 (100) | 36 (100) | 0 | 0 | 0 | 0 | 17 (27.9) | 28 (25.5) | 0 | 8 (13.6) |
| 5–8 | 0 | 0 | 36 (100) | 53 (100) | 0 | 0 | 22 (36.1) | 38 (34.5) | 13 (52.0) | 15 (25.4) |
| ⩾9 | 0 | 0 | 0 | 0 | 34 (100) | 80 (100) | 22 (36.1) | 44 (40.0) | 12 (48.0) | 36 (61.0) |
| **Baseline sputum NE levels** | | | | | | | | | | |
| BLQ | 7 (41.2) | 13 (36.1) | 5 (13.9) | 14 (26.4) | 6 (17.6) | 17 (21.3) | 12 (19.7) | 26 (23.6) | 6 (24.0) | 18 (30.5) |
| LLOQ to <20 μg·mL$^{-1}$ | 7 (41.2) | 15 (41.7) | 24 (66.7) | 25 (47.2) | 11 (32.4) | 24 (30.0) | 30 (49.2) | 46 (41.8) | 12 (48.0) | 18 (30.5) |
| ⩾20 μg·mL$^{-1}$ | 3 (17.6) | 7 (19.4) | 6 (16.7) | 14 (26.4) | 15 (44.1) | 39 (48.8) | 17 (27.9) | 37 (33.6) | 7 (28.0) | 23 (39.0) |
| **$FEV_1$ (% predicted)** | | | | | | | | | | |
| Median (range) | 88.0 (31–116) | 89.0 (53–135) | 71.0 (31–122) n=35 | 67.0 (32–127) | 50.0 (23–88) n=33 | 61.0 (20–105) | 71.0 (29–122) | 67.0 (22–135) | 60.0 (23–108) n=24 | 69.0 (20–115) |
| <50% | 1 (5.9) | 0 | 8 (22.2) | 12 (22.6) | 15 (44.1) | 29 (36.3) | 15 (24.6) | 30 (27.3) | 9 (36.0) | 11 (18.6) |
| **Positive *P. aeruginosa* culture** | 1 (5.9) | 1 (2.8) | 10 (27.8) | 17 (32.1) | 19 (55.9) | 43 (53.8) | 22 (36.1) | 37 (33.6) | 7 (28.0) | 24 (40.7) |
| **Use of inhaled steroids** | 8 (47.1) | 18 (50.0) | 21 (58.3) | 26 (49.1) | 23 (67.6) | 48 (60.0) | 34 (55.7) | 57 (51.8) | 17 (68.0) | 35 (59.3) |
| **Long-term macrolide use** | 0 | 3 (8.3) | 7 (19.4) | 9 (17.0) | 8 (23.5) | 17 (21.3) | 8 (13.1) | 19 (17.3) | 7 (28.0) | 10 (16.9) |
| **Inhaled antibiotics** | 1 (5.9) | 3 (8.3) | 4 (11.1) | 3 (5.7) | 0 | 11 (13.8) | 4 (6.6) | 15 (13.6) | 1 (4.0) | 2 (3.4) |
| **History of COPD** | 2 (11.8) | 1 (2.8) | 7 (19.4) | 4 (7.5) | 8 (23.5) | 20 (25.0) | 13 (21.3) | 12 (10.9) | 4 (16.0) | 13 (22.0) |
| **History of asthma** | 3 (17.6) | 11 (30.6) | 15 (41.7) | 9 (17.0) | 7 (20.6) | 19 (23.8) | 13 (21.3) | 22 (20.0) | 12 (48.0) | 17 (28.8) |
| **PRO** | | | | | | | | | | |
| QoL-B respiratory symptom score | 63 (30–100) n=11 | 59 (33–100) n=32 | 56 (22–78) n=31 | 65 (11–100) n=46 | 41 (11–81) n=31 | 48 (19–96) n=75 | 56 (11–100) n=51 | 56 (11–100) n=100 | 48 (19–78) n=22 | 56 (19–89) n=53 |
| SGRQ total score | 31 (16–66) n=11 | 41 (3–76) n=30 | 48 (17–84) n=34 | 38 (7–71) n=47 | 54 (17–83) | 52 (15–80) n=77 | 46 (16–84) n=54 | 45 (3–77) n=101 | 55 (21–83) n=23 | 48 (15–80) n=53 |

Data are presented as n (%) or median (range), unless otherwise stated. NE: neutrophil elastase; BLQ: below the limit of quantification; LLOQ: lower limit of quantification; $FEV_1$: forced expiratory volume in 1 s; *P. aeruginosa*: *Pseudomonas aeruginosa*; PRO: patient-reported outcome; QoL-B: Quality of Life – Bronchiectasis; SGRQ: St George's Respiratory Questionnaire. [#]: one patient in the placebo group did not have baseline data so analysis was conducted in 255 patients; [¶]: pooled brensocatib 10 mg and 25 mg doses; [+]: race determined by investigator.

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**TABLE 2** Baseline characteristics in WILLOW patients by subgroup: blood eosinophil count, macrolide use and *Pseudomonas aeruginosa* culture subgroups

| Characteristic | Blood eosinophil count[#] | | | | Long-term macrolide use[¶] | | | | *P. aeruginosa* culture[¶] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <300 cells per µL | | ≥300 cells per µL | | No | | Yes | | Negative | | Positive | |
| | Placebo | Brensocatib[+] | Placebo | Brensocatib[+] | Placebo | Brensocatib[+] | Placebo | Brensocatib[+] | Placebo | Brensocatib[+] | Placebo | Brensocatib[+] |
| **Patients, n** | 64 | 142 | 22 | 27 | 72 | 140 | 15 | 29 | 57 | 108 | 30 | 61 |
| **Age, years** | 66.0 (31–84) | 66.0 (22–83) | 67.0 (36–79) | 69.0 (52–80) | 66.5 (32–84) | 66.0 (22–83) | 67.0 (31–73) | 68.0 (28–80) | 66.0 (31–84) | 65.5 (24–83) | 67.0 (45–76) | 68.0 (22–80) |
| **Female sex** | 45 (70.3) | 101 (71.1) | 10 (45.5) | 18 (66.7) | 42 (58.3) | 98 (70.0) | 13 (86.7) | 21 (72.4) | 35 (61.4) | 71 (65.7) | 20 (66.7) | 48 (78.7) |
| **White race[§]** | 53 (82.8) | 128 (90.1) | 17 (77.3) | 26 (96.3) | 58 (80.6) | 128 (91.4) | 13 (86.7) | 26 (89.7) | 47 (82.5) | 99 (91.7) | 24 (80.0) | 55 (90.2) |
| **Exacerbations in prior 12 months** | | | | | | | | | | | | |
| 2 | 50 (78.1) | 94 (66.2) | 11 (50.0) | 16 (59.3) | 53 (73.6) | 91 (65.0) | 8 (53.3) | 19 (65.5) | 39 (68.4) | 73 (67.6) | 22 (73.3) | 37 (60.7) |
| 3 or more | 14 (21.9) | 48 (33.8) | 11 (50.0) | 11 (40.7) | 18 (25.0) | 49 (35.0) | 7 (46.7) | 10 (34.5) | 18 (31.6) | 35 (32.4) | 7 (23.3) | 24 (39.3) |
| **BSI score categories** | | | | | | | | | | | | |
| ≤4 | 15 (23.4) | 33 (23.2) | 2 (9.1) | 3 (11.1) | 17 (23.6) | 33 (23.6) | 0 | 3 (10.3) | 16 (28.1) | 35 (32.4) | 1 (3.3) | 1 (1.6) |
| 5–8 | 25 (39.1) | 44 (31.0) | 10 (45.5) | 9 (33.3) | 29 (40.3) | 44 (31.4) | 7 (46.7) | 9 (31.0) | 26 (45.6) | 36 (33.3) | 10 (33.3) | 17 (27.9) |
| ≥9 | 24 (37.5) | 65 (45.8) | 10 (45.5) | 15 (55.6) | 26 (36.1) | 63 (45.0) | 8 (53.3) | 17 (58.6) | 15 (26.3) | 37 (34.3) | 19 (63.3) | 43 (70.5) |
| **Baseline sputum NE levels** | | | | | | | | | | | | |
| BLQ | 13 (20.3) | 36 (25.4) | 5 (22.7) | 8 (29.6) | 18 (25.0) | 38 (27.1) | 0 | 6 (20.7) | 15 (26.3) | 35 (32.4) | 3 (10.0) | 9 (14.8) |
| LLOQ to <20 µg·mL$^{-1}$ | 33 (51.6) | 53 (37.3) | 9 (40.9) | 11 (40.7) | 34 (47.2) | 56 (40.0) | 8 (53.3) | 8 (27.6) | 30 (52.6) | 44 (40.7) | 12 (40.0) | 20 (32.8) |
| ≥20 µg·mL$^{-1}$ | 16 (25.0) | 52 (36.6) | 8 (36.4) | 8 (29.6) | 18 (25.0) | 45 (32.1) | 6 (40.0) | 15 (51.7) | 12 (21.1) | 28 (25.9) | 12 (40.0) | 32 (52.2) |
| **$FEV_1$ (% predicted)** | | | | | | | | | | | | |
| Median (range) | 73.0 (30–106) | 68.0 (20–127) | 49.0 (23–122) n=21 | 56 (26–135) | 72.0 (29–122) n=70 | 69.0 (20–127) | 46.0 (23–97) | 56.0 (22–135) | 74.0 (31–122) | 74.0 (20–135) | 49.5 (23–111) n=28 | 56.0 (22–126) |
| <50% | 13 (20.3) | 30 (21.1) | 11 (50.0) | 11 (40.7) | 15 (20.8) | 30 (21.4) | 9 (60.0) | 11 (37.9) | 10 (17.5) | 18 (16.7) | 14 (46.7) | 23 (37.7) |
| **Positive *P. aeruginosa* culture** | 20 (31.3) | 47 (33.1) | 9 (40.9) | 14 (51.9) | 22 (30.6) | 43 (30.7) | 8 (53.3) | 18 (62.1) | 0 | 0 | 30 (100) | 61 (100) |
| **Use of inhaled steroids** | 36 (56.3) | 73 (51.4) | 15 (68.2) | 19 (70.4) | 40 (55.6) | 71 (50.7) | 12 (80.0) | 21 (72.4) | 30 (52.6) | 56 (51.9) | 22 (73.3) | 36 (59.0) |
| **Long-term macrolide use** | 9 (14.1) | 21 (14.8) | 6 (27.3) | 8 (29.6) | 0 | 0 | 15 (100) | 29 (100) | 7 (12.3) | 11 (10.2) | 8 (26.7) | 18 (29.5) |
| **Inhaled antibiotics** | 3 (4.7) | 15 (10.6) | 2 (9.1) | 2 (7.4) | 3 (4.2) | 12 (8.6) | 2 (13.3) | 5 (17.2) | 3 (5.3) | 9 (8.3) | 2 (6.7) | 8 (13.1) |
| **History of COPD** | 11 (17.2) | 21 (14.8) | 6 (27.3) | 4 (14.8) | 17 (23.6) | 22 (15.7) | 0 | 3 (10.3) | 11 (19.3) | 16 (14.8) | 6 (20.0) | 9 (14.8) |
| **History of asthma** | 17 (26.6) | 33 (23.2) | 8 (36.4) | 6 (22.2) | 20 (27.8) | 29 (20.7) | 5 (33.3) | 10 (34.5) | 18 (31.6) | 28 (25.9) | 7 (23.3) | 11 (18.0) |
| **PRO** | | | | | | | | | | | | |
| QoL-B respiratory symptom score | 52 (11–100) n=54 | 56 (11–100) n=126 | 52 (19–78) n=19 | 59 (22–89) | 52 (19–100) n=59 | 57 (19–100) n=124 | 46 (11–78) n=14 | 44 (11–100) | 52 (22–100) n=46 | 56 (19–100) n=96 | 52 (11–81) n=27 | 52 (11–100) n=57 |
| SGRQ total score | 47 (16–84) n=57 | 44 (3–80) n=127 | 53 (20–83) n=20 | 48 (18–80) | 47 (16–83) n=63 | 43 (3–80) n=125 | 58 (20–84) n=14 | 53 (14–80) | 50 (16–83) n=49 | 44 (3–79) n=95 | 49 (17–84) n=28 | 48 (7–80) n=59 |

Data are presented as n (%) or median (range), unless otherwise stated. BSI: Bronchiectasis Severity Index; NE: neutrophil elastase; BLQ: below the limit of quantification; LLOQ: lower limit of quantification; $FEV_1$: forced expiratory volume in 1 s; PRO: patient-reported outcome; QoL-B: Quality of Life – Bronchiectasis; SGRQ: St George's Respiratory Questionnaire. [#]: one patient in the placebo group did not have baseline data so analysis was conducted in 255 patients; [¶]: patients for this subgroup were classified based on data from screening; [+]: pooled brensocatib 10 mg and 25 mg doses; [§]: race determined by investigator.

A total of 171 patients (67.1%) experienced two exacerbations in the year prior to enrolment, while 84 (32.9%) experienced three or more exacerbations. Baseline characteristics were generally well balanced between treatment arms in patients experiencing two previous exacerbations apart from sex, race, sputum NE levels, inhaled antibiotic use and history of COPD. In patients who had ⩾3 previous exacerbations, there was some imbalance between treatment groups in race, sputum NE levels, $FEV_1$, *P. aeruginosa* infection, long-term macrolide use, history of COPD or asthma, and PROs (table 1).

A total of 49 patients (19.2%) had an elevated baseline blood eosinophil count (defined as blood eosinophil counts ⩾300 cells per µL). For patients with a blood eosinophil count <300 cells per µL, baseline characteristics between treatment groups were well balanced with some variation in race, number of previous exacerbations, BSI scores, sputum NE levels and inhaled antibiotic use. Baseline characteristics were similar between treatment groups in patients with a blood eosinophil count ⩾300 cells per µL apart from sex, race, BSI and history of COPD or asthma (table 2).

Of the 256 patients, 44 patients (17.2%) had been treated with a macrolide for ⩾6 months (long-term) leading up to study enrolment. In patients with and without macrolide use, there was some variation between treatment groups in sex, number of previous exacerbations, BSI scores, sputum NE levels and history of COPD. Patients with long-term macrolide use also had some imbalance in sputum NE levels, $FEV_1$ and positive *P. aeruginosa* culture (table 2).

At screening, 91 patients (35.5%) had positive *P. aeruginosa* cultures. In patients with and without *P. aeruginosa*, there was some variation in race, BSI score and sputum NE between treatment groups. In patients with positive *P. aeruginosa* cultures, there was also some variation in sex, $FEV_1$ and inhaled corticosteroid (ICS) use (table 2).

Subgroups associated with greater disease severity were associated with other indicators of increased disease severity. For example, patients with higher BSI scores were more likely to have higher baseline levels of sputum NE, to have sputum positive for *P. aeruginosa* at screening, to have received ICS or long-term macrolide treatment, to have a history of COPD and to have worse health-related quality of life (HRQoL). A greater proportion of patients with ⩾3 previous exacerbations had received long-term macrolide treatment or had *P. aeruginosa* cultured from sputum at screening than patients with two previous exacerbations. Patients with a blood eosinophil count ⩾300 cells per µL were more likely than patients with <300 cells per µL to have ⩾3 prior exacerbations, a BSI score ⩾9, use ICS or long-term macrolides, have lower $FEV_1$ or have *P. aeruginosa* in their sputum at screening. Patients receiving long-term macrolide therapy were more likely to have *P. aeruginosa* cultured from sputum at screening, a greater number of previous exacerbations, a lower $FEV_1$, a higher level of sputum NE, a higher BSI score, a history of asthma, worse HRQoL and a higher proportion of ICS use than patients without long-term macrolide treatment. Finally, patients with positive *P. aeruginosa* culture at screening were more likely to have a BSI score ⩾9, a higher level of sputum NE and a history of inhaled steroid, antibiotic or long-term macrolide use.

## *Efficacy outcomes*

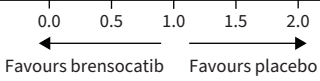
### *Exacerbations*

Across all subgroups, treatment with brensocatib was consistently associated with a reduced risk of exacerbation (as assessed by time to first exacerbation) compared with placebo. The hazard ratio (HR; 95% CI) between patients in the BSI subgroup treated with brensocatib compared with placebo was 0.28 (0.08–0.96) in the BSI ⩽4 subgroup, 0.75 (0.35–1.60) in the BSI 5–8 subgroup and 0.61 (0.35–1.04) in the BSI ⩾9 subgroup (figure 2a). A similar trend was observed in patients treated with brensocatib compared with those treated with placebo who had experienced two exacerbations in the previous year (HR (95% CI) 0.56 (0.34–0.90); figure 2b) and ⩾3 exacerbations in the previous year (HR (95% CI) 0.71 (0.32–1.59)). Patients with a blood eosinophil count of <300 cells per µL had a HR (95% CI) of 0.66 (0.42–1.06) and patients with an eosinophil count of ⩾300 cells per µL had a HR (95% CI) of 0.49 (0.20–1.20) (figure 2c). Regardless of long-term macrolide use, patients had a reduced risk of exacerbation with brensocatib treatment *versus* placebo treatment (HR (95% CI) no long-term macrolide use: 0.60 (0.38–0.94); long-term macrolide use: 0.60 (0.25–1.45)) (figure 2d). In patients with and without a positive *P. aeruginosa* culture at screening, brensocatib was associated with a reduced risk of exacerbation *versus* placebo (HRs (95% CI) of 0.68 (0.37–1.27) and 0.54 (0.32–0.92), respectively; figure 2e).

Annualised exacerbation rates and overall number of exacerbations in the brensocatib-treated arms were consistently lower than those in the placebo arms in all analysed subgroups (figure 2). For patients treated with brensocatib, the annualised exacerbation rate was 62% lower for patients with a BSI score of ⩽4, 31% lower for patients with a BSI score of 5–8, and 31% lower for patients with a BSI score of ⩾9 (figure 2a).

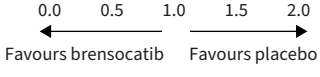
a)

| BSI | Treatment | n | Exacerbations during treatment, n (%) | | | Annualised exacerbation rate, estimate (95% CI) | Rate ratio, (95% CI) | Time to first exacerbation HR (95% CI) | HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| | | | 0 | 1 | ≥2 | | | | |
| ≤4 | Placebo | 17 | 10 (58.8) | 6 (35.3) | 1 (5.9) | 1.47 (0.27–7.88) | 0.38 (0.12–1.15) | | 0.28 (0.08–0.96) |
| | Brensocatib# | 36 | 31 (86.1) | 3 (8.3) | 2 (5.6) | 0.66 (0.14–3.10) | | | |
| 5-8 | Placebo | 36 | 23 (63.9) | 9 (25.0) | 4 (11.1) | 1.10 (0.62–1.98) | 0.69 (0.34–1.40) | | 0.75 (0.35–1.60) |
| | Brensocatib# | 53 | 38 (71.7) | 10 (18.9) | 5 (9.4) | 0.76 (0.44–1.32) | | | |
| ≥9 | Placebo | 34 | 12 (35.3) | 15 (44.1) | 7 (20.6) | 1.95 (1.31–2.91) | 0.69 (0.44–1.11) | | 0.61 (0.35–1.04) |
| | Brensocatib# | 80 | 45 (56.3) | 23 (28.8) | 12 (15.0) | 1.37 (0.99–1.88) | | | |



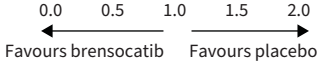

b)

| Exacerbations in prior 12 months | Treatment | n | Exacerbations during treatment, n (%) | | | Annualised exacerbation rate, estimate (95% CI) | Rate ratio, (95% CI) | Time to first exacerbation HR (95% CI) | HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| | | | 0 | 1 | ≥2 | | | | |
| 2 | Placebo | 61 | 29 (47.5) | 25 (41.0) | 7 (11.5) | 1.46 (1.01–2.11) | 0.69 (0.45–1.06) | | 0.56 (0.34–0.90) |
| | Brensocatib# | 110 | 73 (66.4) | 25 (22.7) | 12 (10.9) | 1.01 (0.73–1.39) | | | |
| ≥3 | Placebo | 25 | 15 (60.0) | 5 (20.0) | 5 (20.0) | 1.38 (0.68–2.78) | 0.67 (0.29–1.53) | | 0.71 (0.32–1.59) |
| | Brensocatib# | 59 | 41 (69.5) | 11 (18.6) | 7 (11.9) | 0.93 (0.52–1.64) | | | |



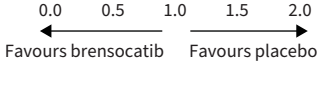

c)

| Blood eosinophil count | Treatment | n | Exacerbations during treatment, n (%) | | | Annualised exacerbation rate, estimate (95% CI) | Rate ratio, (95% CI) | Time to first exacerbation HR (95% CI) | HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| | | | 0 | 1 | ≥2 | | | | |
| <300 cells per µL | Placebo | 64 | 34 (53.1) | 21 (32.8) | 9 (14.1) | 1.49 (1.00–2.21) | 0.74 (0.48–1.14) | | 0.66 (0.42–1.06) |
| | Brensocatib# | 142 | 95 (66.9) | 31 (21.8) | 16 (11.3) | 1.10 (0.81–1.51) | | | |
| ≥300 cells per µL | Placebo | 22 | 10 (45.5) | 9 (40.9) | 3 (13.6) | 1.26 (0.70–2.27) | 0.46 (0.20–1.05) | | 0.49 (0.20–1.20) |
| | Brensocatib# | 27 | 19 (70.4) | 5 (18.5) | 3 (11.1) | 0.58 (0.28–1.20) | | | |




d)

| Chronic macrolide use (≥6 months) | Treatment | n | Exacerbations during treatment, n (%) | | | Annualised exacerbation rate, estimate (95% CI) | Rate ratio, (95% CI) | Time to first exacerbation HR (95% CI) | HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| | | | 0 | 1 | ≥2 | | | | |
| No | Placebo | 72 | 39 (54.2) | 24 (33.3) | 9 (12.5) | 1.36 (0.97–1.90) | 0.69 (0.45–1.06) | | 0.60 (0.38–0.94) |
| | Brensocatib# | 140 | 97 (69.3) | 27 (19.3) | 16 (11.4) | 0.94 (0.71–1.24) | | | |
| Yes | Placebo | 15 | 6 (40.0) | 6 (40.0) | 3 (20.0) | 1.61 (0.89–2.92) | 0.73 (0.33–1.61) | | 0.60 (0.25–1.45) |
| | Brensocatib# | 29 | 17 (58.6) | 9 (31.0) | 3 (10.3) | 1.18 (0.71–1.96) | | | |




e)

| *P. aeruginosa* culture | Treatment | n | Exacerbations during treatment, n (%) | | | Annualised exacerbation rate, estimate (95% CI) | Rate ratio, (95% CI) | Time to first exacerbation HR (95% CI) | HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| | | | 0 | 1 | ≥2 | | | | |
| Negative | Placebo | 57 | 31 (54.4) | 19 (33.3) | 7 (12.3) | 1.58 (1.00–2.50) | 0.64 (0.38–1.08) | | 0.54 (0.32–0.92) |
| | Brensocatib# | 108 | 80 (74.1) | 17 (15.7) | 11 (10.2) | 1.02 (0.67–1.55) | | | |
| Positive | Placebo | 30 | 14 (46.7) | 11 (36.7) | 5 (16.7) | 1.42 (0.89–2.29) | 0.78 (0.45–1.35) | | 0.68 (0.37–1.27) |
| | Brensocatib# | 61 | 34 (55.7) | 19 (31.1) | 8 (13.1) | 1.11 (0.77–1.60) | | | |

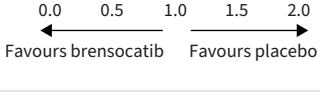



FIGURE 2 Number of exacerbations, annualised exacerbation rates and time to first exacerbations subgroups by a) Bronchiectasis Severity Index (BSI); b) exacerbations in the previous 12 months; c) blood eosinophil count; d) chronic macrolide use; and e) *Pseudomonas aeruginosa* culture. Annualised exacerbation rates were derived using a negative binomial model with the total number of events, onset between the first dose date, and the end of the study as the response variable, treatment, baseline strata and log-transformed time at risk as an offset variable. Time to the first exacerbation was analysed using Kaplan–Meier curves and a stratified-log rank test. CI: confidence interval; HR: hazard ratio. #: pooled brensocatib 10 mg and 25 mg doses.

**TABLE 3** Change in forced expiratory volume in 1 s (mL) from baseline at week 24 in WILLOW patients by subgroup

| Subgroup | Treatment | n | LS means, mL | Difference in LS means, mL | 95% CI |
|---|---|---|---|---|---|
| **BSI** | | | | | |
| ⩽4 | Placebo | 14 | −136.3 (68.2) | 95.7 (71.3) | −46.0–237.3 |
| | Brensocatib# | 32 | −37.4 (46.8) | | |
| 5–8 | Placebo | 30 | −31.4 (44.9) | 35.0 (49.6) | −62.9–133.0 |
| | Brensocatib# | 50 | 3.8 (23.8) | | |
| ⩾9 | Placebo | 30 | −25.3 (25.5) | 7.4 (28.8) | −49.4–64.2 |
| | Brensocatib# | 75 | −17.1 (16.4) | | |
| **Exacerbations in prior 12 months** | | | | | |
| 2 | Placebo | 53 | −71.1 (30.6) | 46.7 (33.7) | −19.7–113.0 |
| | Brensocatib# | 103 | −24.4 (15.7) | | |
| ⩾3 | Placebo | 21 | 8.4 (31.9) | −6.7 (34.8) | −75.6–62.1 |
| | Brensocatib# | 54 | 2.1 (19.8) | | |
| **Blood eosinophil count** | | | | | |
| <300 cells per µL | Placebo | 56 | −60.9 (27.3) | 46.2 (29.8) | −12.4–104.8 |
| | Brensocatib# | 134 | −14.6 (14.4) | | |
| ⩾300 cells per µL | Placebo | 18 | −16.2 (51.7) | 6.1 (57.6) | −108.5–120.8 |
| | Brensocatib# | 23 | −9.7 (25.1) | | |
| **Long-term macrolide use (⩾6 months)** | | | | | |
| No | Placebo | 60 | −49.4 (27.4) | 38.0 (30.0) | −21.0–97.0 |
| | Brensocatib# | 133 | −11.4 (14.3) | | |
| Yes | Placebo | 14 | −24.0 (49.5) | 17.0 (56.8) | −96.2–130.2 |
| | Brensocatib# | 24 | −7.1 (26.3) | | |
| ***P. aeruginosa* culture status** | | | | | |
| Negative | Placebo | 48 | −50.2 (32.7) | 32.4 (34.8) | −36.1–100.8 |
| | Brensocatib# | 101 | −17.7 (17.1) | | |
| Positive | Placebo | 26 | −37.7 (35.0) | 41.2 (40.9) | −39.5–122.0 |
| | Brensocatib# | 56 | 3.5 (19.2) | | |

Data are presented as mean (SE), unless otherwise stated. BSI: Bronchiectasis Severity Index; CI: confidence interval; LS: least squares; *P. aeruginosa*: *Pseudomonas aeruginosa*. #: pooled brensocatib 10 mg and 25 mg doses.

When analysed by exacerbation frequency, both patients who had experienced two or ⩾3 exacerbations in the previous year had a lower annualised exacerbation rate if they had received brensocatib compared with those who had received placebo (31% and 33% lower, respectively; figure 2b). Similarly, the annualised exacerbation rate was lower for patients treated with brensocatib regardless of blood eosinophil counts (26% and 54% lower for patients with <300 eosinophils per µL and ⩾300 eosinophils per µL, respectively; figure 2c) or long-term macrolide use (31% and 27% lower with no long-term macrolide use and long-term macrolide use, respectively; figure 2d). *P. aeruginosa* culture subgroups also showed decreased annualised exacerbation rates (36% and 22% lower for patients with negative and positive screening culture, respectively; figure 2e). A higher proportion of patients treated with brensocatib also experienced no exacerbations across all subgroups during the study.

### *Lung function ($FEV_1$)*

After the 24-week treatment period, lung function decline was numerically lower in brensocatib-treated patients compared with placebo across all subgroups analysed (table 3). Differences in least square means between brensocatib- and placebo-treated patients were generally greater in patients with more mild disease (mL difference (SE) for patients with BSI ⩽4, 95.7 (71.3); two previous exacerbations, 46.7 (33.7); blood eosinophil count <300 cells per µL, 46.2 (29.8); and no long-term macrolide use, 38.0 (30.0)).

### *Safety*

The incidence of TEAEs was similar across subgroups, and consistent with results from all treatment groups (supplementary table S1).

## Discussion

Non-CF bronchiectasis is a heterogeneous disease in both aetiology and outcomes [3, 9, 16]. Patients present with differing severity of disease, exacerbation history and inflammatory endotype, and may

receive differing treatment regimens despite longstanding guidelines [14, 16]. Current treatments do not directly target neutrophilic inflammation, a key driver of non-CF bronchiectasis pathophysiology and disease progression [17]. Inconsistent results have been observed in recent clinical trials that focused on targeting chronic infection by respiratory pathogens, including *P. aeruginosa* in patients with non-CF bronchiectasis [18–21]. However, for the future development of anti-inflammatory therapies, it is important to identify whether targeting inflammation in subgroups of patients is a more appropriate approach.

We performed *post hoc* analyses on data from the WILLOW trial to assess the efficacy of targeting downstream mediators of neutrophil-mediated inflammation, including NSPs, with brensocatib in patients with non-CF bronchiectasis with differing baseline characteristics. We used multiple factors to address the complexity of the disease (disease severity by BSI scores, exacerbation phenotype, *P. aeruginosa* infection and blood eosinophil count) along with other indicators such as long-term macrolide use, which is recommended for patients with frequent exacerbations [14]. All examined subgroups responded to treatment with brensocatib, with numerically longer time to first exacerbation and reduced frequency of exacerbations compared with placebo. Lung function decline was also numerically lower in patients treated with brensocatib *versus* placebo; however, any observed numerical differences in effect on lung function between individual subgroups should not be interpreted as clinically meaningful given that these are *post hoc* analyses.

Overall, 19.2% of patients with non-CF bronchiectasis had blood eosinophil counts ⩾300 cells per µL, which is highly consistent with the observations of Shoemark *et al*. [9] in multiple European cohorts. An important observation was that patients with elevated blood eosinophil counts at baseline had similar NE levels to patients with lower baseline blood eosinophil counts. This suggests that rather than there being "neutrophilic" and "eosinophilic" subgroups of non-CF bronchiectasis, patients with eosinophilic inflammation have concomitant, clinically significant neutrophilic inflammation and, consistent with this observation, still derived a benefit when treated with brensocatib compared with placebo. Additionally, patients with an elevated blood eosinophil count had more severe disease, with a higher proportion having ⩾3 exacerbations in the previous year. These findings are consistent with a recent report by Choi *et al*. [11], which demonstrated that mixed neutrophilic and eosinophilic inflammation was common and associated with increased exacerbations based on cluster analysis on airway inflammation profiles in patients with non-CF bronchiectasis.

An interesting finding of our analysis was that, while there was a trend toward benefit from brensocatib treatment across all subgroups, the largest relative benefit was seen in patients with mild non-CF bronchiectasis (BSI ⩽4). It is important to note that although these patients had milder disease per their BSI score, all patients in the WILLOW trial had ⩾2 exacerbations in the year prior to enrolment, with exacerbations themselves being the most important clinical predictor of future exacerbations [3]. Patients with a BSI ⩽4 also had the lowest sputum NE levels. Recent work has identified that patients who suppressed sputum NE levels below the limit of quantification on treatment had the greatest benefit in terms of reduced exacerbations [22]. If replicated in the ongoing brensocatib phase III ASPEN trial (NCT04594369; EudraCT number: 2020-003688-25), this has important implications as interventions in non-CF bronchiectasis are often reserved for severe disease, but these preliminary data suggest a high level of benefit may be achieved by targeting patients at an earlier stage of disease.

The safety profile in this study was consistent across subgroups and reflected what was observed overall in the WILLOW study.

This study has some limitations. The trial was only 6 months in duration and included only 256 participants. Due to the small patient numbers and the lack of stratification based on the subgroup factors, subgroup sizes were variable and this may have influenced the results observed. These *post hoc* results were descriptive and, to increase the size of subgroups, based on pooled brensocatib doses with similar efficacy as observed overall in the WILLOW trial. However, WILLOW was not adequately powered to observe differences in efficacy between doses, and consequently these *post hoc* analyses were not powered to detect statistical differences between the included subgroups, some of which were very small. Future studies should focus on assessing the efficacy of brensocatib in subgroups based on disease severity with larger patient cohorts.

## Conclusions

Brensocatib showed efficacy in preventing exacerbations in patients with mild, moderate and severe non-CF bronchiectasis, in patients with and without *P. aeruginosa* infection, on top of long-term macrolide therapy, and in patients with co-occurring eosinophilic inflammation, suggesting a broad potential for benefit across disease phenotypes and endotypes. Results in all subgroups were consistent with the

WILLOW results overall. The ongoing phase III ASPEN trial (NCT04594369) is evaluating the safety and efficacy of a longer treatment duration (52 weeks) with brensocatib in a larger cohort of patients with non-CF bronchiectasis (over 1600 patients).

Provenance: Submitted article, peer reviewed.

Data availability: Data collected for this study will not be made available to others.

This study is registered at www.clinicaltrials.gov with identifier number NCT03218917.

Ethics statement: The study was conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki, with protocol approval from local institutional review boards and independent ethics committees.

Conflict of interest: J.D. Chalmers reports receiving grants and personal fees from AstraZeneca, Boehringer Ingelheim, GSK, Zambon and Insmed Incorporated, a grant from Gilead, and personal fees from Novartis and Chiesi; and is an associate editor of this journal. M.R. Loebinger reports receiving consulting fees from 30T, AN2 Therapeutics, Armata, AstraZeneca, Boehringer Ingelheim, Chiesi, Electromed, Insmed Incorporated, MannKind, Parion Sciences, Recode Therapeutics, Savara and Zambon. A. Teper, C. Fernandez, S. Fucile, M. Lauterio and V.H. Shih are employees of and shareholders in Insmed Incorporated. R. van der Laan was an employee of Insmed Incorporated at the time of this study. P.J. McShane is site primary investigator for clinical trials with the following pharmaceutical companies: AN2 Therapeutics, Armata, Boehringer Ingelheim, Insmed Incorporated, Paratek and Renovion; and reports trial steering committee membership for Boehringer Ingelheim and Insmed Incorporated; and consulting fee from Insmed Incorporated. C.S. Haworth reports receiving consultancy/speaker fees from 30 Technology, AstraZeneca, CSL Behring, Chiesi, Infex, Insmed Incorporated, Janssen, LifeArc, Mylan, Pneumagen, Shionogi, Tactile Medical, Vertex and Zambon. M.L. Metersky reports receiving consulting fees from AN2 Therapeutics, Boehringer Ingelheim, Insmed Incorporated, Renovion, Tactile Inc. and Zambon.

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