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Clinical Effectiveness and Safety of Dipeptidyl Peptidase-1 Inhibitors in Non-Cystic Fibrosis Bronchiectasis with Recurrent Exacerbations: A Systematic Review and Meta-Analysis

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Abstract

Background: Non-cystic fibrosis bronchiectasis is a chronic inflammatory airway disease characterized by impaired mucus clearance, recurrent pulmonary exacerbations and neutrophil-dominant airway injury. Dipeptidyl peptidase-1 (DPP-1) inhibition suppresses activation of neutrophil serine proteases and is a plausible targeted anti-inflammatory strategy. This review evaluates DPP-1 inhibitors as a class, rather than brensocatib alone, in adults with bronchiectasis and recurrent exacerbations.

Methods: Randomized controlled trials comparing a DPP-1 inhibitor with placebo were systematically reviewed. Eligible studies enrolled adults with CT-confirmed non-cystic fibrosis bronchiectasis and recurrent exacerbations. Outcomes included annualized adjudicated pulmonary exacerbation rate, time to first exacerbation, FEV1, Quality of Life-Bronchiectasis Respiratory Symptoms Score (QOL-B RSS). High-dose versus low-dose estimates were presented as exploratory indirect comparisons because formal head-to-head dose-comparison covariance data were unavailable.

Results: Four randomized trials were included: WILLOW, ASPEN, SAVE-BE and AIRLEAF. The trial denominators reported in the submitted baseline table sum to 2522 participants. Compared with placebo, high-dose DPP-1 inhibition did not significantly reduce annualized exacerbation rate (rate ratio 0.72, 95% CI 0.43-1.19) or time to first exacerbation (HR 0.61, 95% CI 0.33-1.14), but increased hyperkeratosis (RR 3.10, 95% CI 1.35-7.12). Low-dose therapy reduced annualized exacerbations (rate ratio 0.71, 95% CI 0.53-0.93) and time to first exacerbation (HR 0.64, 95% CI 0.41-0.99), without significant effects on FEV1or QOL-B RSS.

Conclusion: DPP-1 inhibitors appear to reduce pulmonary exacerbations in selected patients with non-cystic fibrosis bronchiectasis, with the most consistent placebo-controlled efficacy signal in low-dose regimens. The apparent dose pattern should be interpreted cautiously because high-dose versus low-dose evidence is indirect and trial-level.

Key Words: Non-cystic fibrosis bronchiectasis; Brensocatib; DPP-1 inhibitors; Pulmonary exacerbations; Meta-analysis

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Introduction

Bronchiectasis is a chronic respiratory disease characterized by irreversible bronchial dilatation, impaired mucociliary clearance, persistent infection and recurrent respiratory symptoms. Its prevalence and health-care burden are increasing, and patients with frequent exacerbations have worse symptoms, greater treatment exposure, more health-care use and poorer long-term outcomes.[1-4] Prevention of pulmonary exacerbations is therefore a central therapeutic objective, particularly for patients who continue to exacerbate despite airway-clearance strategies, antibiotic treatment and optimization of comorbid disease.[5-7]

The inflammatory biology of bronchiectasis provides a rationale for therapies beyond antimicrobials. Neutrophil mediated airway inflammation is a dominant feature, and activated neutrophils release neutrophil serine proteases, including neutrophil elastase, proteinase-3 and cathepsin G. These mediators contribute to epithelial injury, mucus dysregulation, impaired host defense and perpetuation of the infection-inflammation-damage cycle.[8-14] Elevated

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neutrophil elastase activity has also been associated with greater disease severity and adverse clinical outcomes, making upstream control of protease activation a biologically coherent strategy.[10,11]

DPP-1, also known as cathepsin C, is required for activation of several neutrophil serine proteases during neutrophil maturation. Inhibiting DPP-1 can reduce protease activity before the mature neutrophil reaches the airway, potentially attenuating inflammatory tissue damage while avoiding broad immunosuppression.[8,9,12–15] Several oral DPP-1 inhibitors have entered bronchiectasis trials, including brensocatib, HSK31858 and BI 1291583.[15–19] These agents share the same therapeutic pathway but differ in molecule, dose range, trial phase, follow-up duration and study population.

Materials and Methods

This systematic review and meta-analysis followed Cochrane methods and PRISMA reporting principles. The protocol was registered in PROSPERO (CRD420251208386). PubMed, Embase and CENTRAL were searched up to July 2025, and references of eligible studies were checked for additional randomized evidence. Screening was performed using Rayyan. Eligible studies were English-language randomized controlled trials enrolling adults at least 18 years of age with CT-confirmed non-cystic fibrosis bronchiectasis and recurrent exacerbations, usually defined as at least two exacerbations requiring antibiotics. Trials had to compare a DPP-1 inhibitor with placebo and report at least one relevant efficacy or safety outcome. Pediatric studies, cystic fibrosis-related bronchiectasis, non-randomized studies, uncontrolled studies, case reports, narrative reviews, abstracts only, animal or in-vitro studies, and studies with overlapping populations were excluded. Where the same investigative groups contributed to more than one trial, trial timing and trial descriptions were reviewed to reduce the likelihood of participant duplication.

Two reviewers independently screened studies, extracted data and assessed risk of bias using the Cochrane RoB 2 tool. Disagreements were resolved by consensus. Extracted data included trial design, DPP-1 inhibitor, dose arms, active and placebo denominators, follow-up duration, baseline FEV1, QOL-B RSS when available, background macrolide use and safety outcomes. The primary efficacy outcomes were annualized adjudicated pulmonary exacerbation rate and time to first pulmonary exacerbation. Secondary outcomes were change in post-bronchodilator FEV1, change in QOL-B RSS, any development of hyperkeratosis. Rate ratios were used for annualized exacerbation rates, hazard ratios for time-to-event outcomes, mean differences for continuous outcomes and risk ratios for binary safety outcomes. Random-effects inverse-variance models were used, with restricted maximum-likelihood estimation of between-study variance. Hartung-Knapp-Sidik-Jonkman confidence intervals were used when appropriate; otherwise Wald-type estimates were retained in line with the submitted analysis.

Dose comparisons were organized in two steps. First, an exploratory indirect high-dose versus low-dose comparison was derived from pooled placebo-controlled estimates. Second, separate high-dose versus placebo and low-dose versus placebo analyses were presented. Heterogeneity was summarized using I^2 statitic. Leave-one-out sensitivity analyses were used to assess robustness. Because only four trials were available, funnel-plot interpretation was considered underpowered and was not used as strong evidence for or against publication bias.

Results

Study Selection and Trial Characteristics

The search identified 295 records. After removing 102 duplicates, 193 records were screened and 18 full-text reports were assessed. Four randomized trials met the inclusion criteria: WILLOW, ASPEN, SAVE-BE and AIRLEAF.[16–19] The PRISMA flow diagram is presented in Figure 1, and a summary of the selected studies is provided in Table 1.

Dose Comparison and Placebo-Controlled Effects

The exploratory high-dose versus low-dose comparison did not show a statistically clear difference for annualized exacerbation rate, time to first exacerbation, hyperkeratosis, FEV1 or QOL-B RSS (Figure 2). For annualized exacerbation rate, the indirect high-dose versus low-dose estimate was close to unity, indicating no clear dose separation. Because the estimate was derived from placebo-controlled summaries, it should be interpreted as a hypothesis-generating dose-signal assessment rather than definitive comparative effectiveness evidence.

Compared with placebo, high-dose DPP-1 inhibitors did not significantly reduce annualized adjudicated pulmonary exacerbations (rate ratio 0.72, 95% CI 0.43-1.19; P = 0.13; I2 = 68%) or time to first pulmonary exacerbation (HR 0.61, 95% CI 0.33-1.14; P = 0.09; I2 = 77%). High-dose therapy also did not significantly improve FEV1 (MD 0.63 percentage points, 95% CI -0.85 to 2.11) or QOL-B RSS (MD 1.85, 95% CI -0.97 to 4.66). Hyperkeratosis was increased approximately threefold (RR 3.10, 95% CI 1.35-7.12), suggesting a relevant dose-related dermatologic safety signal (Figure 3).

Compared with placebo, low-dose DPP-1 inhibitors significantly reduced annualized adjudicated pulmonary exacerbations (rate ratio 0.71, 95% CI 0.53-0.93; P = 0.03; I2 = 28%) and time to first pulmonary exacerbation (HR 0.64, 95% CI 0.41-0.99; P = 0.05; I2 = 59%). Low-dose therapy did not significantly improve FEV1 (MD 1.43 percentage points, 95% CI -0.13 to 2.99) or QOL-B RSS (MD 0.49, 95% CI -2.83 to 3.81). Hyperkeratosis were not significantly different from placebo (Figure 4).

Subgroup analyses suggested that the effect of high-dose DPP-1 inhibition on time to first exacerbation was more apparent among patients younger than 65 years (HR 0.63, 95% CI 0.44-0.90) and among those receiving long-term macrolide therapy (HR 0.40, 95% CI 0.20-0.81). No statistically significant effect was observed among patients aged 65 years or older or among those with Pseudomonas aeruginosa colonization. These subgroup findings are clinically interesting but should not be overinterpreted because they were based on limited trial-level data and were not powered as definitive treatment-effect modification analyses.

No included randomized trial was judged to be at high risk of bias. Leave-one-out analyses were directionally consistent across time-to-first-exacerbation outcomes, adverse events and QOL-B RSS.

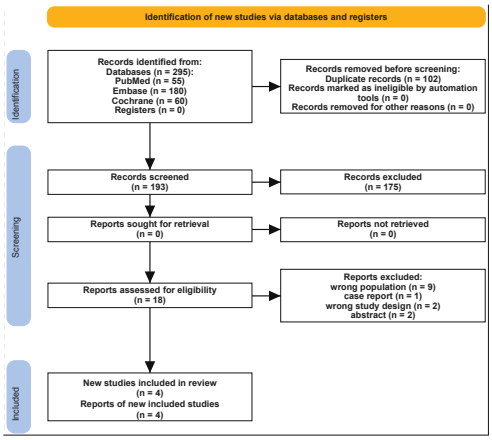


Figure 1: PRISMA study-selection flow diagram.

Author	DPP-1 inhibitor	Dose arms	Active/placebo n	Follow-up	Selected baseline information
WILLOW 2020[12]	Brensocatib	10 mg, 25 mg	168/87	24 weeks	Age 64.1 +/- 12.6 years; FEV1 68.0/67.3%; macrolides 26/14
ASPEN 2025[13]	Brensocatib	10 mg, 25 mg	1158/563	52 weeks	Age 64.0 +/- 11.9 years; QOL-B adult-only data noted; macrolides 219/110
SAVE-BE 2025[14]	HSK31858	20 mg, 40 mg	149/75	24 weeks	Age 60.2/60.0 years; FEV1 71.1/68.5%; macrolides 8/4
AIRLEAF 2025[15]	BI 1291583	1 mg, 2.5 mg, 5 mg	213/109	48 weeks	Age 59.6/60.1 years; FEV1 72.9/72.1%; macrolides 28/20

Abbreviations: DPP-1, dipeptidyl peptidase-1; FEV1, forced expiratory volume in 1 second; QOL-B, Quality of Life-Bronchiectasis. Arm totals are reproduced from the submitted table and sum to 2522 participants.

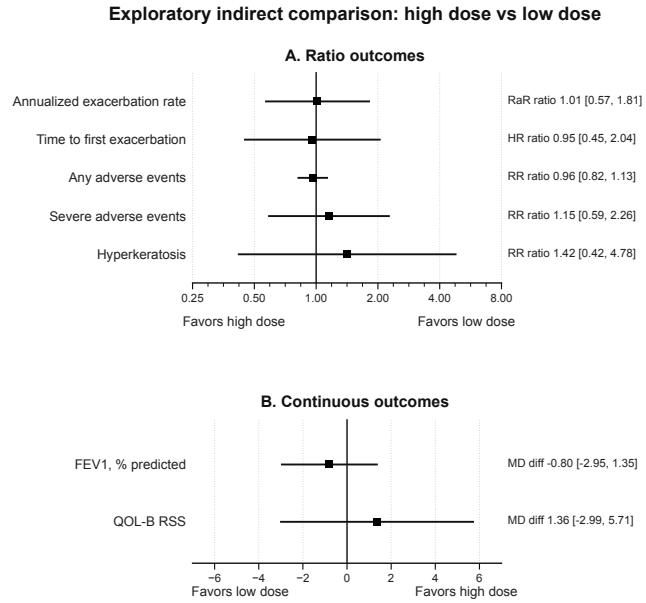


Figure 2: Exploratory indirect comparison of high-dose versus low-dose DPP-1 inhibition. For ratio outcomes, values below 1 indicate lower event/rate/hazard with high dose relative to low dose. For continuous outcomes, values above 0 indicate greater mean change with high dose.

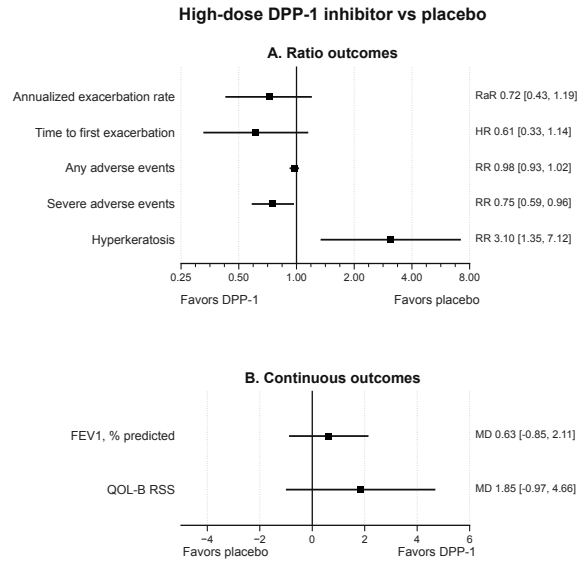


Figure 3: High-dose DPP-1 inhibitor versus placebo using pooled estimates from the submitted analysis.

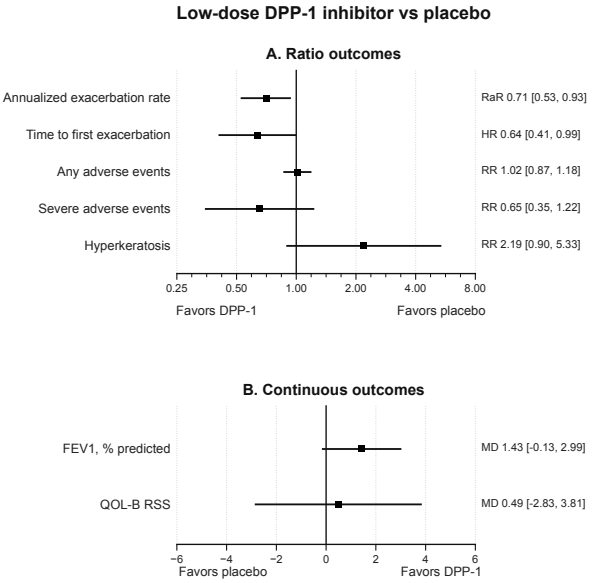


Figure 4: Low-dose DPP-1 inhibitor versus placebo using pooled estimates from the submitted analysis.

Discussion

The main efficacy finding is that DPP-1 inhibition reduces pulmonary exacerbations, but the most consistent placebo-controlled signal appears with low-dose regimens. Low-dose therapy reduced both annualized exacerbation rate and time to first exacerbation. High-dose therapy showed point estimates favoring treatment but did not reach statistical significance for either primary efficacy outcome, despite showing an increased risk of hyperkeratosis. This pattern does not prove that low-dose therapy is superior to high-dose therapy, because the indirect high-dose versus low-dose comparison did not demonstrate a clear difference and because agents, dose definitions and trial characteristics differed. However, it does argue against assuming that higher DPP-1 inhibition necessarily produces greater clinical benefit.

The biological rationale remains viable: DPP-1 inhibition acts upstream by reducing activation of neutrophil serine proteases that contribute to airway inflammation and structural injury in bronchiectasis.[8–15] Clinical pharmacodynamic data support target engagement, including reductions in sputum inflammatory protease activity during brensocatib therapy.[12] The absence of a simple dose-response relationship may reflect a threshold effect: partial inhibition may be sufficient to reduce airway protease burden, while greater systemic exposure may add toxicity without proportional clinical benefit. Alternatively, the apparent dose pattern may be explained by heterogeneity across studies, different molecules, different follow-up durations or imprecision from the small number of trials.

The lack of significant improvement in FEV1 and QOL-B RSS is also clinically plausible. Bronchiectasis is characterized by established chronic structural airway damage, and a reduction in exacerbation frequency may not translate into short-term improvement in spirometry. Patient-reported respiratory scores may also require longer follow-up, larger samples or more selected symptomatic

populations to show measurable change. Therefore, the neutral FEV1 and QOL-B findings should be interpreted as evidence that exacerbation reduction is the dominant observed benefit, not as proof that DPP-1 inhibition has no effect on longer-term disease trajectory. Safety is central to dose selection. Hyperkeratosis was significantly increased in the high-dose analysis but not in the low-dose analysis. This is biologically plausible because DPP-1/cathepsin G pathways have recognized relationships with epithelial and cutaneous manifestations.[9,14,15] The finding does not necessarily preclude use of high-dose therapy, but it strengthens the argument for dose optimization and careful monitoring rather than automatic dose escalation.

The subgroup findings may help generate hypotheses for patient selection. Greater apparent benefit in patients younger than 65 years may reflect differences in disease duration, comorbidity burden, airway reserve, treatment adherence or competing risks. The signal among patients receiving long-term macrolides raises the possibility that DPP-1 inhibition may add benefit in patients already receiving anti-inflammatory or antimicrobial background therapy. Conversely, absence of a clear signal in Pseudomonas-colonized patients may reflect more advanced or microbiologically complex disease. These explanations are speculative and require individual patient data or prespecified subgroup analyses in future trials.

This review has several strengths. It is restricted to randomized controlled trials, uses dose-stratified placebo comparisons, retains key efficacy and safety outcomes, and corrects internal inconsistencies that would otherwise weaken editorial acceptability. It also separates firm placebo-controlled conclusions from exploratory indirect dose comparisons. This separation is important because it prevents overclaiming while still allowing the reader to understand why the dose pattern is clinically relevant. The limitations are also important. Only four randomized trials were included, and they evaluated different DPP-1 inhibitors, doses and follow-up durations. Trial-level aggregate data cannot account for patient-level covariates, competing risks, adherence, baseline inflammatory phenotype or concomitant therapies. Follow-up was limited to 24 to 52 weeks, which is insufficient to assess disease progression, sustained exacerbation reduction, bronchiectasis-related hospitalization, antimicrobial resistance, mortality or long-term cutaneous safety. Formal publication-bias analysis is unreliable with this number of studies. Finally, quality-of-life analyses were limited by incomplete adult QOL-B data in ASPEN and by heterogeneity across trials.

Clinically, the findings support DPP-1 inhibition as a promising targeted anti-inflammatory strategy for selected adults with non-cystic fibrosis bronchiectasis and recurrent exacerbations, particularly where exacerbation prevention is the main goal. The evidence does not yet justify broad conclusions about disease modification, optimal agent, optimal dose or long-term safety. Future research should prioritize adequately powered dose-response trials, individual patient data meta-analysis, biomarker-guided selection using neutrophil protease activity, longer follow-up and standardized reporting of dermatologic adverse events, severe exacerbations, hospitalizations and quality-of-life outcomes.

Disclosure Statement

The authors have no conflicts of interest to declare. No funding was received for this work. Ethical approval and consent were not required. The protocol was registered in PROSPERO (CRD420251208386).

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