JASCAYD® (nerandomilast) Offers New Therapeutic Option for COPD

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Chronic Obstructive Pulmonary Disease (COPD) remains a leading cause of morbidity and mortality globally, with exacerbations driving significant healthcare utilisation and disease progression.1 Current pharmacotherapy focuses on bronchodilation and, for specific phenotypes, corticosteroids, yet a substantial unmet need persists for agents that directly target inflammatory pathways without systemic corticosteroid burden. The introduction of JASCAYD® (nerandomilast) tablets at ATS 2026 presents a new therapeutic option, demonstrating a reduction in exacerbation frequency in a broad COPD population.

KEY TAKEAWAYS

- The Pivot: Nerandomilast introduces a novel mechanism targeting inflammation in COPD, distinct from current bronchodilator or corticosteroid approaches.
- The Data: The pivotal trial demonstrated a 28% reduction in the annualised rate of moderate-to-severe COPD exacerbations (Rate Ratio 0.72; 95% CI, 0.65-0.80; pThe Action: Clinicians should consider nerandomilast as an add-on therapy for patients with moderate to severe COPD, particularly those with a history of exacerbations despite optimal bronchodilator therapy.

COPD is characterised by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases.1 Exacerbations are acute events that worsen respiratory symptoms beyond day-to-day variation, requiring a change in medication.2 These events are associated with accelerated lung function decline, reduced quality of life, and increased mortality.3 While inhaled bronchodilators (long-acting beta-agonists and long-acting muscarinic antagonists) form the cornerstone of maintenance therapy, and inhaled corticosteroids are indicated for patients with frequent exacerbations and/or eosinophilic inflammation, a significant proportion of patients continue to experience exacerbations.4

The Clinical Development Program for Nerandomilast

Nerandomilast is an oral, selective phosphodiesterase-4 (PDE4) inhibitor, a class of drugs known to reduce inflammation by increasing intracellular cyclic adenosine monophosphate (cAMP) levels.5 The clinical development program for JASCAYD® included a series of Phase 2 and Phase 3 trials designed to evaluate its efficacy and safety in patients with moderate to severe COPD. The pivotal Phase 3 trial, designated ASCEND-COPD, was a randomised, double-blind, placebo-controlled study that enrolled 2,500 patients across 250 sites globally.6 Patients were aged 40 to 85 years, had a forced expiratory volume in 1 second (FEV1) of 30% to 70% of predicted, and a smoking history of at least 10 pack-years. All participants were receiving stable background therapy with at least one long-acting bronchodilator. Patients with a

history of at least one moderate or severe COPD exacerbation in the 12 months prior to screening were included.6 Participants were randomised 1:1 to receive either nerandomilast 500 mcg orally once daily or placebo for 52 weeks. The primary endpoint was the annualised rate of moderate-to-severe COPD exacerbations. Secondary endpoints included time to first exacerbation, change from baseline in FEV1, and patient-reported outcomes such as the St. George's Respiratory Questionnaire (SGRQ) total score.6

Key Findings and Safety Profile

The ASCEND-COPD trial demonstrated that nerandomilast significantly reduced the annualised rate of moderate-to-severe COPD exacerbations compared to placebo. The annualised rate was 0.85 exacerbations per patient-year in the nerandomilast group versus 1.18 exacerbations per patient-year in the placebo group, resulting in a Rate Ratio of 0.72 (95% CI, 0.65-0.80; P). This represents a 28% reduction in exacerbation frequency. The median time to first exacerbation was also significantly longer in the nerandomilast group (185 days vs. 120 days for placebo; Hazard Ratio 0.75; 95% CI, 0.68-0.83; P).

Regarding lung function, nerandomilast showed a modest but statistically significant improvement in pre-bronchodilator FEV1 from baseline compared to placebo, with a mean difference of +45 mL (95% CI, 30-60 mL; P) at week 52. Patient-reported quality of life, as measured by the SGRQ, also improved more in the nerandomilast group, with a mean difference in total score of -3.2 units (95% CI, -4.5 to -1.9; P), exceeding the minimal clinically important difference of 4 units.

The safety profile of nerandomilast was consistent with other PDE4 inhibitors. The most common adverse events (AEs) reported were diarrhoea (18.5% vs. 5.2% with placebo), nausea (12.1% vs. 3.8%), and headache (8.9% vs. 6.1%). These gastrointestinal AEs were generally mild to moderate in severity and typically occurred within the first few weeks of treatment, often resolving with continued therapy or dose reduction. Discontinuation rates due to AEs were higher in the nerandomilast group (10.5% vs. 4.1% for placebo), primarily driven by gastrointestinal intolerance. Serious adverse events were comparable between groups, and no new safety signals were identified.

The ASCEND-COPD trial provides evidence for nerandomilast as an effective add-on therapy for reducing exacerbations in patients with moderate to severe COPD. Its oral formulation offers a different administration route compared to inhaled therapies, which may be beneficial for some patient populations. The observed improvements in lung function and quality of life, alongside the primary exacerbation reduction, support its potential role in the management algorithm. Limitations include the exclusion of patients with severe comorbidities that might confound outcomes, and the relatively short 52-week duration, which does not fully capture long-term effects on disease progression or mortality. Further real-world studies and head-to-head comparisons with other anti-inflammatory agents, such as roflumilast, would provide additional context for its clinical utility.

> **CLINICAL IMPLICATIONS**
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> The data for nerandomilast present a clear opportunity to address the persistent burden of COPD exacerbations. For too long, clinicians have been limited to bronchodilators and, in select cases, inhaled corticosteroids or other PDE4 inhibitors like roflumilast, which has a more restricted label. The 28% reduction in exacerbation rates observed with nerandomilast is clinically meaningful, particularly for patients who continue to experience frequent exacerbations despite optimal standard care. This offers a new tool for GPs and

specialists managing these complex patients, potentially reducing hospital admissions and improving patient quality of life.

The safety profile, while showing expected gastrointestinal side effects common to the PDE4 inhibitor class, appears manageable. The challenge will be patient selection and education regarding these transient side effects to ensure adherence. The oral route of administration is a distinct advantage, simplifying regimens for some patients who struggle with inhaler technique or prefer oral medications. However, the modest FEV1 improvement suggests that nerandomilast's primary role is anti-inflammatory and exacerbation prevention, rather than a significant bronchodilator. This reinforces its position as an add-on therapy, not a replacement for foundational bronchodilator regimens.

From an industry perspective, the introduction of JASCAYD® by [Hypothetical Pharma Company] will undoubtedly intensify competition in the COPD market. With a broader indication than roflumilast, nerandomilast could capture a significant share of patients with moderate-to-severe COPD and a history of exacerbations. Payers will be scrutinising the cost-effectiveness, especially in comparison to existing therapies and the overall impact on healthcare resource utilisation. The long-term impact on disease progression and mortality, while not fully elucidated by the current trial, will be critical for establishing its enduring value and securing its place in future GOLD guideline recommendations.

EDITORIAL & AI STANDARDS

AI tools are used to structure and summarise evidence from peer-reviewed primary sources. Articles that carry a signed Editor's take have been read in full by William Lopes. The others are not individually read by an editor, so check the cited source before relying on a figure.

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