Trends in Pharmacological Sciences | Drug of the Month

Nerandomilast as the first PDE4B-selective therapy in idiopathic pulmonary fibrosis

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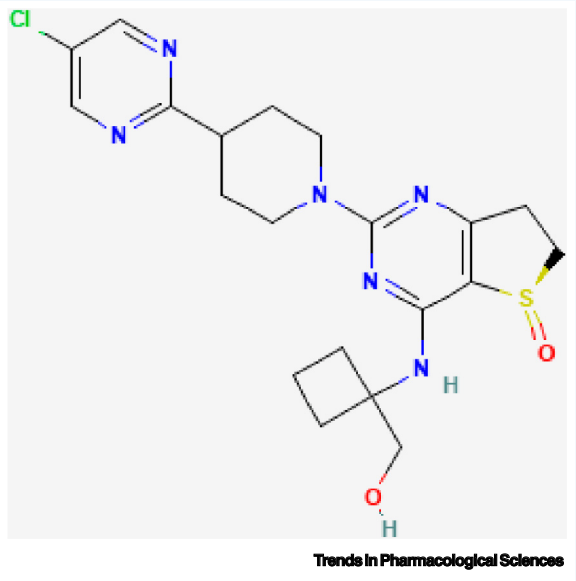
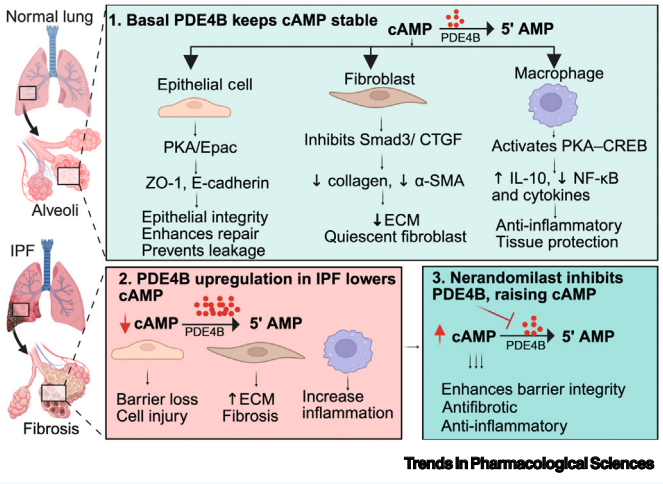


STRUCTURE: Nerandomilast is a small-molecule thienopyrimidine sulfoxide derivative that contains a thieno[3,2-d] pyrimidin-5-one core substituted with a (5-chloropyrimidin-2-yl)piperidinyl group and an (R)-hydroxymethyl-cyclobutylamino side chain. This structural arrangement confers high affinity and selectivity for the PDE4B isoform while minimizing off-target inhibition of other PDE4 subtypes. The sulfoxide (S) stereochemistry and the (5R) configuration at the cyclobutyl center are essential for PDE4B selectivity. The empirical formula is $C_{20}H_{25}ClN_6O_2S$, and the molecular weight is 449 g/mol.



MECHANISM OF ACTION: Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive interstitial lung disease caused by repetitive epithelial injury and defective epithelial wound repair, creating an imbalance between tissue injury and regeneration. This imbalance leads to persistent inflammation, fibroblast activation, and excessive extracellular matrix (ECM) deposition, resulting in irreversible remodeling and distortion of the alveolar structure.

NAME:
Nerandomilast (BI 1015550) is commercially available under the trade name JASCAYD™.

DRUG CLASS:
Nerandomilast is a first-in-class, oral phosphodiesterase-4 (PDE4) inhibitor with preferential (≥9-fold) inhibition of PDE4B over PDE4A/C/D.

CLINICAL USE:
Nerandomilast is approved for adults with IPF. It is taken orally at 18 mg twice daily, with or without food. If not tolerated, the dose may be reduced to 9 mg twice daily, except when used with pirfenidone, where the full dose should be maintained. Tablets may be swallowed whole or dispersed in water for patients with swallowing difficulties.

DEVELOPED BY:
Developed by Boehringer Ingelheim International GmbH, nerandomilast, is the result of over two decades of research into PDE4 biology, inflammation, and fibrosis that identified PDE4B as a key therapeutic target in IPF.

ADVERSE EFFECTS:
In the Phase 3 FIBRONEER-IPF trial, the most common adverse reactions to nerandomilast were diarrhea (42%), coronavirus disease 2019 (COVID-19) infection (13%), upper respiratory tract infection (13%), depression (12%), weight decrease (11%), decreased appetite (9%), and nausea (8%). Less frequent events included fatigue, headache, vomiting, and dizziness (5–7%). Diarrhea was generally mild to moderate, occurred early in treatment, and was more frequent when combined with nintedanib. Weight loss and decreased appetite were also more common with concomitant antifibrotic therapy. Overall, adverse events were consistent with those associated with PDE4 inhibition and were manageable with dose adjustment or supportive care.

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Current antifibrotic therapies, including nintedanib and pirfenidone, have been shown to slow the loss of lung function but fail to halt disease progression. Thus, many patients continue to experience declining lung capacity and adverse effects that lead to dose reduction or discontinuation. Phosphodiesterase 4 (PDE4) enzymes regulate intracellular cyclic AMP (cAMP), a second messenger that suppresses inflammatory and fibrotic signaling. The PDE4 family includes four subtypes: PDE4A, PDE4B, PDE4C, and PDE4D. These subtypes differ in their tissue distribution and biological roles. Among them, PDE4B is highly expressed in lung macrophages and fibroblasts, where it promotes cytokine release and fibroblast proliferation. Nerandomilast preferentially inhibits PDE4B, which in turn prevents the breakdown of cAMP and helps restore intracellular signaling balance. Elevated cAMP levels reduce the production of proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6. They also reduce fibroblast proliferation, myofibroblast differentiation, and collagen deposition. By targeting the early interaction between immune and fibrotic pathways rather than downstream tyrosine kinase or transforming growth factor (TGF)-β signaling, orally administered nerandomilast exerts both anti-inflammatory and antifibrotic effects in an oral formulation. The overall outcome is preservation of alveolar integrity and a measurable slowing of disease progression.

Acknowledgments

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Declaration of interests

F.A. discloses partial ownership of MedLuidics LLC, located in Elk Grove, CA. M.I. discloses partial ownership of Oncovask Therapeutics LLC in Elk Grove, CA, and confirms no other conflicts of interest to disclose. The contents reported/presented within do not represent the views of the Department of Veterans Affairs or the US Government.

Literature

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TIMELINE:

2012–2021: Phase 1 safety and pharmacokinetic (PK) studies in healthy volunteers (NCT01835899, NCT03302078, NCT04771286, NCT01594515).

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2018–2019: Dose-ranging IPF study assessing PK and tolerability (NCT03422068).

2020–2021: Phase 2 IPF trial showing maintenance of lung function (NCT04419506).

Feb 2022: FDA grants Breakthrough Therapy Designation for BI 1015550.

2022–2025: Phase 3 FIBRONEER-IPF (NCT05321069) and FIBRONEER-PPF (NCT05321082) trials confirm efficacy and safety.

Sep 2024: FIBRONEER-IPF meets primary endpoint (52-week FVC decline).

Oct 2025: FDA approval of JASCAYD™ (nerandomilast) for adult IPF.

2024–present: Long-term extension FIBRONEER-ON (NCT06238622) ongoing.

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