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# Ziritaxestat, a Novel Autotaxin Inhibitor, and Lung Function in Idiopathic Pulmonary Fibrosis

## The ISABELA

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# 1 and 2 Randomized Clinical Trials

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*JAMA.* 2023;329(18):1567-1578. doi:10.1001/jama.2023.5355

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## Key Points

**Question** Does the autotaxin inhibitor ziritaxestat improve outcomes, compared with placebo, in patients with idiopathic pulmonary fibrosis who continue to receive standard of care with pirfenidone, nintedanib, or neither standard of care treatment?

**Findings** In 2 randomized clinical trials, ISABELA 1 and ISABELA 2, there was no reduction in the 52-week rate of decline for forced vital ca-

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pacity (a measure of lung function) in the 2 ziritaxestat groups vs placebo, and combined data from both trials showed all-cause mortality rates were numerically higher for ziritaxestat than placebo. Therefore, the trials were stopped early.

**Meaning** The autotaxin inhibitor ziritaxestat was ineffective as a treatment for idiopathic pulmonary fibrosis.

## Abstract

**Importance** There is a major need for effective, well-tolerated treatments for idiopathic pulmonary fibrosis (IPF).

**Objective** To assess the efficacy and safety of the autotaxin inhibitor ziritaxestat in patients with IPF.

**Design, Setting, and Participants** The 2 identically designed, phase 3, randomized clinical trials, ISABELA 1 and ISABELA 2, were conducted in Africa, Asia-Pacific region, Europe, Latin America, the

Middle East, and North America (26 countries). A total of 1306 patients with IPF were randomized (525 patients at 106 sites in ISABELA 1 and 781 patients at 121 sites in ISABELA 2). Enrollment began in November 2018 in both trials and follow-up was completed early due to study termination on April 12, 2021, for ISABELA 1 and on March 30, 2021, for ISABELA 2.

**Interventions** Patients were randomized 1:1:1 to receive 600 mg of oral ziritaxestat, 200 mg of ziritaxestat, or placebo once daily in addition to local standard of care (pirfenidone, nintedanib, or neither) for at least 52 weeks.

**Main Outcomes and Measures** The primary outcome was the annual rate of decline for forced vital capacity (FVC) at week 52. The key secondary outcomes were disease progression, time to first respiratory-related hospitalization, and change

from baseline in St George's Respiratory Questionnaire total score (range, 0 to 100; higher scores indicate poorer health-related quality of life).

**Results** At the time of study termination, 525 patients were randomized in ISABELA 1 and 781 patients in ISABELA 2 (mean age: 70.0 [SD, 7.2] years in ISABELA 1 and 69.8 [SD, 7.1] years in ISABELA 2; male: 82.4% and 81.2%, respectively). The trials were terminated early after an independent data and safety monitoring committee concluded that the benefit to risk profile of ziritaxestat no longer supported their continuation. Ziritaxestat did not improve the annual rate of FVC decline vs placebo in either study. In ISABELA 1, the least-squares mean annual rate of FVC decline was -124.6 mL (95% CI, −178.0 to −71.2 mL) with 600 mg of ziritaxestat vs -147.3 mL (95% CI, −199.8 to −94.7 mL) with placebo (between-group difference,

22.7 mL [95% CI, −52.3 to 97.6 mL]), and -173.9 mL (95% CI, −225.7 to −122.2 mL) with 200 mg of ziritaxestat (between-group difference vs placebo, −26.7 mL [95% CI, −100.5 to 47.1 mL]). In ISABELA 2, the least-squares mean annual rate of FVC decline was -173.8 mL (95% CI, −209.2 to −138.4 mL) with 600 mg of ziritaxestat vs -176.6 mL (95% CI, −211.4 to −141.8 mL) with placebo (between-group difference, 2.8 mL [95% CI, −46.9 to 52.4 mL]) and -174.9 mL (95% CI, −209.5 to −140.2 mL) with 200 mg of ziritaxestat (between-group difference vs placebo, 1.7 mL [95% CI, −47.4 to 50.8 mL]). There was no benefit with ziritaxestat vs placebo for the key secondary outcomes. In ISABELA 1, all-cause mortality was 8.0% with 600 mg of ziritaxestat, 4.6% with 200 mg of ziritaxestat, and 6.3% with placebo; in ISABELA 2, it was 9.3% with 600 mg of ziritaxestat, 8.5% with 200

mg of ziritaxestat, and 4.7% with placebo.

**Conclusions and Relevance**
Ziritaxestat did not improve clinical outcomes compared with placebo in patients with IPF receiving standard of care treatment with pirfenidone or nintedanib or in those not receiving standard of care treatment.

**Trial Registration** ClinicalTrials.gov Identifiers: NCT03711162 and NCT03733444

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