Ziritaxestat, a Novel Autotaxin Inhibitor, and Lung Function in Idiopathic Pulmonary Fibrosis The ISABELA 1 and 2 Randomized Clinical Trials

Peer-reviewed author version

Maher, Toby M.; Ford, Paul; Brown, Kevin K.; Costabel, Ulrich; Cottin, Vincent; Danoff, Sonye K.; Groenveld, Irene; Helmer, Eric; Jenkins, R. Gisli; Milner, Julie; MOLENBERGHS, Geert; Penninckx, Bjorn; Randall, Matthew J.; Van den Blink, Bernt; Fieuw, Ann; Vandenrijn, Charlotte; Rocak, Sanda; Seghers, Ineke; Shao, Lixin; Taneja, Amit; Jentsch, Garrit; Watkins, Timothy R.; WUYTS, Tim; Kreuter, Michael; Verbruggen, Nadia; Prasad, Niyati & Wijsenbeek, Marlies S. (2023) Ziritaxestat, a Novel Autotaxin Inhibitor, and Lung Function in Idiopathic Pulmonary Fibrosis The ISABELA 1 and 2 Randomized Clinical Trials. In: JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 329 (18) , p. 1567 -1578.

DOI: 10.1001/jama.2023.5355
Handle: http://hdl.handle.net/1942/40541

1. Title page

Effect of Ziritaxestat, a Novel Autotaxin Inhibitor, vs Placebo on Lung Function in Idiopathic Pulmonary Fibrosis: The ISABELA 1 and 2 Randomized Clinical Trials

Toby M. Maher, MD, PhD[1,2], Paul Ford, MD, PhD[3], Kevin K. Brown, MD[4], Ulrich Costabel, MD, PhD[5], Vincent Cottin, MD, PhD[6], Sonye K. Danoff, MD, PhD[7], Irene Groenveld, MSc[8, 9], Eric Helmer, Pharm D[10, 11], R. Gisli Jenkins, MD, PhD[12], Julie Milner, PhD[13, 14], Geert Molenberghs, PhD[15], Bjorn Penninckx, MD[3], Matthew J. Randall, PhD[16], Bernt Van Den Blink, MD, PhD[8], Ann Fieuw, MD[3], Charlotte Vandenrijn, RN[3], Sanda Rocak, PhD[16], Ineke Seghers, MSc[3, 17], Lixin Shao, MD, MS[13], Amit Taneja, MD, PhD[18], Garrit Jentsch, PhD[19], Timothy R. Watkins, MD, MSc[13], Wim A. Wuyts, MD, PhD[20], Michael Kreuter, MD[21, 22, 23], Nadia Verbruggen, MSc[3], Niyati Prasad, MBBS, MSc, DPM[3, 25], Marlies S. Wijsenbeek, MD, PhD[25]

Affiliations

1. National Heart and Lung Institute, Imperial College London, London, UK

2. Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

3. Galapagos NV, Mechelen, Belgium

4. National Jewish Health, Denver, CO, USA

5. Center for Interstitial and Rare Lung Diseases, Ruhrlandklinik, University Medicine Essen, Essen, Germany

6. Reference Center for Rare Pulmonary Diseases, Hôpital Louis Pradel, Hospices Civils de Lyon, and IVPC, INRAE, Claude Bernard University Lyon 1, Lyon, France;
ORCID # 0000-0002-5591-0955

7. Johns Hopkins Medicine, Baltimore, MD, USA

8. Galapagos NV, Leiden, the Netherlands

9. CellPoint BV, Oegstgeest, the Netherlands

10. Galapagos Biotech Limited, Cambridge, UK

11. Exscientia, Oxford, UK

12. National Heart and Lung Institute, Imperial College London, London, UK

13. Gilead Sciences, Inc., Foster City, CA, USA

14. Alnylam, Maidenhead, UK

15. Hasselt University, Hasselt, and KU Leuven, Leuven, Belgium

16. Galapagos GmbH, Basel, Switzerland

17. Argenx, Gent, Belgium

18. Galapagos SASU, Romainville, France

19. BAST GmbH, Heidelberg, Germany

20. Department of Respiratory Medicine, Unit for Interstitial Lung Diseases, University Hospitals Leuven, Leuven, Belgium

21. Center for Interstitial and Rare Lung Diseases, Pneumology, Thoraxklinik, University Hospital Heidelberg, Heidelberg, Germany

22. German Center for Lung Research, Heidelberg, Germany

23. Center for Pulmonary Medicine, Departments of Pneumology, Mainz University Medical Center and of Pulmonary, Critical Care & Sleep Medicine, Marienhaus Clinic Mainz, Mainz, Germany

24. Enterprise Therapeutics, Brighton, UK

25. Centre for Interstitial Lung Diseases and Sarcoidosis, Department of Respiratory Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands

Corresponding author: Toby M. Maher

Address: Keck School of Medicine, University of Southern California, 1510 San Pablo Street, Los Angeles, CA 90033, USA (toby.maher@med.usc.edu); Telephone: +1 650 278 0058; ORCiD iD: orcid.org/0000-0001-7192-9149

Word count: 4135

Key Points

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

Findings: In two clinical trials, ISABELA 1 and 2, no reduction in the 52-week rate of decline in forced vital capacity (a measure of lung function) was seen in the ziritaxestat groups versus placebo, and combined data from both studies 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 IPF.

2. Abstract

Importance: There is a major unmet 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: ISABELA 1 and 2 were two identically designed, randomized, double-blind, placebo-controlled phase 3, global studies, conducted in Europe, the Middle East and Africa, Latin America, North America and Asia-Pacific. 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. In ISABELA 1 and 2, respectively, enrollment began on 28 November, 2018 and 05 November, 2018 and follow-up was completed early due to study termination on 12 April, 2021 and 30 March 2021.

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

Main Outcomes and Measures: The primary endpoint was annual rate of decline of forced vital capacity (FVC). Key secondary endpoints were disease progression, time to first respiratory-related hospitalization and change from baseline in St George's Respiratory Questionnaire total score (which ranged from 0 to 100, with higher scores indicating poorer health-related quality of life). Other secondary endpoints included time to respiratory-related mortality, time to all-cause mortality or respiratory-related hospitalization, time to first acute IPF exacerbation, change from baseline in FVC, 6-minute walk test distance and safety and tolerability.

Results: At the time of study termination, 525 and 781 patients were randomized, in ISABELA 1 and 2 respectively (mean [SD] age: 70.0 [7.2] and 69.8 [7.1] years; male: 82.4% and 81.2%, respectively). The trials were terminated early after an independent data

Commented [OGT1]: "Time to exacerbation" is not included here, but it is included in the "Other secondary outcomes" section of the text.

monitoring committee concluded that the benefit–risk profile of ziritaxestat no longer supported their continuation. Ziritaxestat did not improve the annual rate of FVC decline versus placebo in either study: in ISABELA 1 the least-squares mean (95% CI) annual rate of FVC decline was –124.6 mL (−178.0, −71.2) with ziritaxestat 600 mg vs –147.3 mL (−199.8, −94.7) with placebo (difference [95% CI]: 22.7 [−52.3, 97.6]), and –173.9 mL (−225.7, −122.2) with ziritaxestat 200 mg (difference vs placebo [95% CI]: −26.7 [−100.5, 47.1]. In ISABELA 2 the least-squares mean (95% CI) annual rate of FVC decline was–173.8 mL (−209.2, −138.4) with ziritaxestat 600 mg vs –176.6 mL (−211.4, −141.8) with placebo (difference [95% CI] 2.8 [−46.9, 52.4]) and –174.9 mL (−209.5, −140.2) with ziritaxestat 200 mg (difference vs placebo [95% CI] 1.7 [−47.4, 50.8]). There was no benefit with ziritaxestat versus placebo for key secondary outcomes. In ISABELA 1, all-cause mortality was 8.0% and 4.6% with ziritaxestat 600 mg and 200 mg, respectively, and 6.3% with placebo (hazard ratio [95% CI] vs placebo: 1.4 [0.6, 3.1] and 0.7 [0.3, 1.8]); in ISABELA 2, it was 9.3% and 8.5% with ziritaxestat 600 mg and 200 mg, respectively, and 4.7% with placebo (hazard ratio [95% CI] vs placebo: 2.1 [1.1, 4.3] and 1.9 [0.9, 3.8]).

Conclusions and Relevance: Ziritaxestat did not improve clinical outcomes compared with placebo in patients with IPF receiving standard of care treatment with pirfenidone, nintedanib, or neither.

Trial Registration: ClinicalTrials.gov Identifiers: NCT03711162; NCT03733444.

3. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease associated with progressive and irreversible fibrosis, dyspnea, lung function decline and loss of quality of life.[1,2] Median survival without treatment is approximately 3 years, with respiratory failure being the most frequent cause of death.[3] While treatment with pirfenidone or nintedanib slows disease progression, patients continue to suffer loss of lung function and premature death.[4] Furthermore, in a substantial proportion of patients, pirfenidone and nintedanib are associated with adverse effects, which may lead to treatment discontinuation.[5] Thus, there remains a major unmet need for more effective, better tolerated IPF treatments.

Pulmonary fibrosis in IPF is believed to develop when aberrant responses to lung injury, including epithelial apoptosis and fibroblast recruitment, occur.[6-8] Lysophosphatidic acid (LPA) is thought to be at least partially responsible for mediating such responses.[6,7] Autotaxin, an enzyme involved in the production of LPA,[9] is upregulated in patients with IPF and is therefore a potential target for novel IPF therapies.[6,10] Ziritaxestat (GLPG1690) is a small-molecule, selective autotaxin inhibitor,[11-15] which showed promising results in a phase 2a study conducted in 23 patients with IPF.[16] Ziritaxestat was well tolerated and those treated with ziritaxestat demonstrated a smaller mean change from baseline in forced vital capacity (FVC) at Week 12 versus placebo. Further, ziritaxestat reduced the concentration of plasma LPA, with a maximum reduction from baseline of approximately 90%, confirming target engagement.[16]

To further evaluate the efficacy and safety of ziritaxestat for the treatment of IPF, ISABELA 1 and 2 (NCT03711162; NCT03733444), two identically designed phase 3 IPF studies were subsequently conducted.

4. Methods

4.1. Study design and eligibility criteria

ISABELA 1 and 2 were randomized, double-blind, placebo-controlled, global studies(eFigure 1; see Supplement for protocol and statistical analysis plan).[17] Patients were recruited from pulmonary clinics; patients were recruited from 106 sites in 14 countries in ISABELA 1 and from 121 sites in 15 countries in ISABELA 2. Eligible men or women were aged ≥40 years and had been diagnosed with IPF within the previous 5 years. IPF diagnosis was confirmed through central review of a high-resolution computed tomography scan of the chest performed within the 12 months prior to screening and lung biopsy (if available). At the time of enrollment, patients were receiving treatment with local standard of care (SoC; a stable dose of pirfenidone or nintedanib for at least 2 months prior to screening, or neither therapy). Eligible patients had to be able to walk ≥150 m in the 6-minute walk test at screening visit 1. At visit 2, resting arterial oxygen saturation ($Sp0_2$) had to be ≥88% with a maximum of 6 L 0_2/min for the oxygen titration test; during the walk, $Sp0_2$ had to be ≥83% with 6 L 0_2/min or ≥88% with 0, 2, or 4 L 0_2/min. Additional inclusion criteria included FVC ≥45% predicted of normal, forced expiratory volume in 1 second (FEV_1)/FVC ≥0.7, and diffusing capacity of the lung for carbon monoxide (DLCO) corrected for hemoglobin ≥30% predicted of normal. Exclusion criteria included immunosuppressive conditions (e.g. HIV, congenital, acquired or medication induced); hepatitis B or C positive serology; malignancy within the past 5 years (except for carcinoma in situ of the uterine cervix, basal carcinoma of the skin that shows no evidence of recurrence following treatment, prostate cancer that has been medically managed with active surveillance or watchful waiting, squamous cell carcinoma of the skin if fully resected, and Ductal Carcinoma in situ); certain medications (e.g., strong inducers or inhibitors of CYP3A4, and potent inducers or inhibitors of P-gp); acute IPF exacerbation within 6 months; lower respiratory tract infection requiring antibiotics within 4 weeks; severe pulmonary hypertension; lung volume reduction surgery or lung transplant; interstitial lung disease with known primary diseases (such as sarcoidosis or amyloidosis), exposures (such

as radiation) or drugs (such as amiodarone); unstable cardiovascular, pulmonary (other than IPF), or other disease within 6 months; creatine clearance <30 mL/min; hemoglobin level <10 g/dL; alcohol or substance abuse; pregnancy; abnormal liver function test. Patients attended two screening visits; at Visit 1 assessments included inclusion and exclusion criteria, demographics, medical history, alcohol consumption and smoking habits, St George's Respiratory Questionnaire (SGRQ), electrocardiogram, $Sp0_2$ test, spirometry, DLCO, adverse events, prior and concomitant medication, physical examination and vital signs, blood sampling, and the six-minute walk test. Assessments at the second screening visit were spirometry, $Sp0_2$ test, oxygen titration test for the six-minute walk test, adverse events and concomitant medication. Patients were randomized at Visit 3. Following randomization patients were assessed at Weeks 2, 4, 8, 12, 18, 26, 34, 42 and 52. Spirometry assessments were performed at each of these visits and then every 12 weeks; blood samples for pharmacokinetic/pharmacodynamic assessments were collected at Week 12, 26, 34 and 52 and then every 24 weeks. If patients could not attend study sites due to the COVID-19 pandemic, study visits were conducted virtually or via phone calls.

In both studies, patients were randomized 1:1:1 to receive oral ziritaxestat 600 mg, ziritaxestat 200 mg or matching placebo once daily on top of local SoC until the last patient completed 52 weeks, to allow the collection of long-term efficacy and safety data. Initiation of pirfenidone or nintedanib or switching SoC during the studies was allowed. Treatment was allocated to each patient using a centralized electronic system (interactive web-based response system) with permuted blocks. Both patients and study personnel were blinded to treatment allocation. Randomization was stratified by local SoC for IPF (nintedanib or pirfenidone) or neither, and recruitment could be restricted in one or more strata, while the other strata continue to recruit to maintain a balanced proportion of patients between the three strata. Clinical study personnel monitored the amount of study drug dispensed to a patient and the amount returned to assess treatment compliance. For doses taken at home, the intake was reported using patient diary cards. The study drug was to be discontinued if

aspartate transaminase or alanine transaminase levels exceeded 8 times the upper limit of normal or were ≥3 times the upper limit of normal with signs of severe liver damage.

The studies were conducted in accordance with the Declaration of Helsinki and local ethical and legal requirements. Study protocols were approved by the independent ethics committee/institutional review board for each site or country, as applicable. All patients provided written informed consent. Enrollment began in November 2018; the studies were terminated early in February 2021.

4.2. Endpoints

The primary endpoint was annual rate of FVC decline up to Week 52. Key secondary endpoints were: disease progression (a composite endpoint of first occurrence of ≥10% absolute decline in percent predicted FVC or all-cause mortality at Week 52); time to first respiratory-related hospitalization until the end of the study; and change from baseline in SGRQ total score at Week 52. Other secondary endpoints included time to respiratory-related mortality, time to all-cause mortality or respiratory-related hospitalization, time to first acute IPF exacerbation, change from baseline in FVC, 6-minute walk test distance and safety and tolerability over time until the end of the study (**eMethods**).

Data were reviewed by an independent data monitoring committee (IDMC) and Clinical Endpoint Adjudication Committee (CEAC). The IDMC assessed potential safety risks and examined unblinded FVC data to assess the effect of treatment on lung function so a recommendation could be made to the study sponsor regarding study continuation. The IDMC regularly reviewed the data (every 3 to 4 months) ; and in addition, an interim futility analysis was planned once at least 25% of patients from the two studies combined had completed 52 weeks of treatment. However, the studies were terminated after the 6th regular data review, before the interim futility analysis occurred. The CEAC adjudicated major events, including exacerbations, hospitalizations and deaths, based on blinded data.

4.3. Pharmacokinetic and pharmacodynamic assessments

Pharmacokinetic assessments included the plasma concentration of ziritaxestat, pirfenidone and nintedanib. Target engagement (autotaxin inhibition) was determined by LPA C18:2 plasma concentration. Modelling was performed to determine exposure–response relationships (**eMethods**).[18]

4.4. Statistical analyses

The full analysis set was used for primary and safety analyses and comprised all randomized patients who received at least one dose of study drug. Assuming ziritaxestat 600 mg had an effect on FVC of ≥80 mL versus placebo, a sample size of 250 per group would provide 80% power to show a significant effect. Therefore, each study was expected to enroll 750 patients (250 patients in the ziritaxestat 600 mg, ziritaxestat 200 mg and placebo groups).

For the primary endpoint, a random coefficient regression model (linear slope model[19]) was used, which included sex, age, height and stratification factor as covariates and a random slope and intercept. A protocol-defined sensitivity analysis was performed to assess annual rate of FVC decline up to the end of the trials using all study data and a post hoc sensitivity analysis was performed to assess FVC decline up to the end of the trials using all study data according to treatment strata.

Logistic regression analysis was used to assess the proportion of patients with disease progression at Week 52. Time-to-event data are presented as Kaplan–Meier estimates. A Cox proportional hazards model was used to estimate and test hazard ratios (HRs) for each dose of ziritaxestat versus placebo. A mixed-effect model was applied to the SGRQ total score (**eMethods**). To account for multiple testing due to two doses of ziritaxestat being compared with placebo, a Bonferroni approach was used with higher priority given to the high-dose group. The primary endpoint was tested at the alpha 4% and 1% level when comparing ziritaxestat 600 mg and 200 mg, respectively, with placebo. The rate of decline

model, which assumes a linear trend over time, was applied to all available data. Therefore, imputation of missing data was not performed.

5. Results

5.1. Study termination

The studies were terminated early,. following a planned review of pooled unblinded data by the IDMC. The IDMC concluded that there were safety concerns regarding increased mortality in the ziritaxestat 600 mg group, and a lack of efficacy in all treatment arms and therefore the benefit–risk profile of ziritaxestat no longer supported the continuation of the studies. At that time, 1116 and 1431 patients had been screened in ISABELA 1 and 2, respectively.

5.2. Patient disposition and baseline characteristics

In ISABELA 1 and 2, 525 and 781 patients were randomized and 523 and 777 received at least one dose of their assigned study drug, respectively (**Figure 1**). After the premature termination of the trials all patients discontinued study drug (**Figure 1**). At the time of study termination, enrollment was ongoing in ISABELA 1 and had completed in ISABELA 2.

The median duration between HRCT scan and study enrollment was 51 days overall in ISABELA 1 (41, 58 and 60 days in the ziritaxestat 600 mg, ziritaxestat 200 mg and placebo groups, respectively) and 50 days overall in ISABELA 2 (64, 50 and 43 days in the ziritaxestat 600 mg, ziritaxestat 200 mg and placebo groups, respectively). In the ziritaxestat 600 mg, ziritaxestat 200 mg and placebo groups, 20, 27 and 19 lung biopsies were reviewed, respectively, in ISABELA 1, as were 28, 33 and 28, respectively, in ISABELA 2. In each study, baseline demographics and disease characteristics were similar in the ziritaxestat 600 mg, 200 mg and placebo groups (**Table 1**). There was a greater proportion of Asian patients in ISABELA 2 than ISABELA 1 (28.1% vs 5.5%) owing to the geographical

location of sites. Mean baseline FVC and percent predicted FVC were slightly higher in ISABELA 1 than ISABELA 2 (2921.1 mL vs 2764.7 mL and 79.3% vs 77.3%, respectively); a higher proportion of patients in ISABELA 2 were former smokers (71.4% vs 61.6%) (**Table 1**).

Upon enrollment in ISABELA 1, 39.8% and 34.6% of patients were taking pirfenidone and nintedanib, respectively, while 25.6% received neither. In ISABELA 2, 32.4% and 34.9% of patients were taking pirfenidone and nintedanib, respectively, while 32.7% received neither (**Table 1**). The mean dose of pirfenidone at enrollment was 2216 mg/day in ISABELA 1 (2184, 2165 and 2300 mg/day in the ziritaxestat 600 mg, ziritaxestat 200 mg and placebo groups, respectively) and 2083 mg/day in ISABELA 2 (2020, 2031 and 2201 mg/day in the ziritaxestat 600 mg, ziritaxestat 200 mg and placebo groups, respectively). The mean dose of nintedanib at enrollment was 283 mg/day in ISABELA 1 (293, 278 and 278 mg/day in the ziritaxestat 600 mg, ziritaxestat 200 mg and placebo groups, respectively) and 267 mg/day in ISABELA 2 (262, 270 and 270 mg/day in the ziritaxestat 600 mg, ziritaxestat 200 mg and placebo groups, respectively). Of patients taking neither pirfenidone nor nintedanib at the time of enrollment, 79.1% and 68.1% in ISABELA 1 and 2, respectively, had never been treated with either therapy. Mean IPF duration was shorter in the group taking neither pirfenidone nor nintedanib (1.8 years in both ISABELA 1 and 2) than in the pirfenidone (2.4 years and 2.6 years in ISABELA 1 and 2, respectively) or nintedanib strata (2.4 years in both ISABELA 1 and 2) (**eTable 1**). Percent predicted FVC was slightly lower in patients who received either pirfenidone or nintedanib (75.0–77.4%) than in those who received neither (85.6% in ISABELA 1; 79.9% in ISABELA 2) (**eTable 1**).

5.3. Treatment duration and exposure

Treatment exposures were longer in ISABELA 2 than in ISABELA 1 (**eTable 2)**, reflecting that the patients were followed up for longer on average. Treatment compliance was high in all treatment groups (median was 100% in each treatment arm in both ISABELA 1 and 2;

eTable 2). The dose of nintedanib was reduced or interrupted in a greater proportion of patients in the ziritaxestat 600 mg group than ziritaxestat 200 mg or placebo groups (**Table 2**); in the ziritaxestat 600 mg group, the proportion of patients who underwent dose reductions or interruptions of SoC was greater in the nintedanib stratum than pirfenidone stratum (**Table 2**). Diarrhea was the most common TEAE leading to nintedanib dose reductions (ISABELA 1: 6.7%, 4.9% and 3.3% in the ziritaxestat 600 mg, ziritaxestat 200 mg and placebo groups, respectively; ISABELA 2: 22.5%, 6.6% and 8.8% in each group, respectively) or interruptions (ISABELA 1: 10.0%, 8.2% and 6.7% in the ziritaxestat 600 mg, ziritaxestat 200 mg and placebo groups, respectively; ISABELA 2: 22.5%, 13.2% and 8.8% in each group, respectively). Mean daily doses of pirfenidone and nintedanib are given in **eTable 3**. During ISABELA 1 and 2, respectively, 5.0% and 5.9% of patients switched from nintedanib to pirfenidone, while 1.9% and 1.6% switched from pirfenidone to nintedanib. In ISABELA 1 and 2, respectively, 11.9% and 9.1% of patients who were assigned ziritaxestat alone (i.e. not on top of pirfenidone or nintedanib) initiated SoC during the studies (**eTable 4**).

5.4. Primary endpoint: annual rate of FVC decline

Ziritaxestat did not improve annual rate of FVC decline versus placebo (**Table 3**). In ISABELA 1, the least-squares (LS) mean (standard error [SE]) annual rate of FVC decline up to Week 52 was –124.6 (27.2) mL with ziritaxestat 600 mg, –173.9 (26.3) mL with ziritaxestat 200 mg and –147.3 (26.7) mL with placebo. Corresponding data for ISABELA 2 were –173.8 (18.0) mL with ziritaxestat 600 mg, –174.9 (17.7) mL with ziritaxestat 200 mg and –176.6 (17.7) mL with placebo. Pooled data from both studies are shown in **Table 3**. Similar results were observed in the sensitivity analysis, which included all data until the end of the studies; when analyzed by stratum, annual rate of FVC decline was greatest in the pirfenidone group (**Table 3**). In each trial, the treatment–stratum–time interaction p-value was <0.001 indicating a significant interaction. For the primary endpoint, 19 patients (1%) from the full analysis set (N=1281) were excluded from the linear slope model analysis due

to missing post-baseline FVC data. At Week 52, FVC data were missing for 92 patients (17%).

5.5. Key secondary endpoints

At Week 52, disease progression was similar across treatment arms, both when data from ISABELA 1 and 2 were pooled and assessed separately (**eFigure 2**).

For time to first respiratory-related hospitalization outcomes were worse in the ziritaxestat arm versus placebo in both ISABELA 1 and 2 (**eFigure 3)**; reasons for hospitalization are shown in **eTable 5**. Change from baseline in SGRQ total score at Week 52 was similar across treatment groups in each study (**eTable 6**).

5.6. Other secondary endpoints

For the following endpoints, worse outcomes were observed with ziritaxestat versus placebo: time to respiratory-related mortality, time to all-cause mortality or respiratory-related hospitalization, or time to first acute IPF exacerbation (**eFigures 4–6**).

Pooled study data showed observed mean change from baseline in FVC was similar across treatment arms at Week 52 (**eFigure 7**). Changes from baseline in FVC per stratum are shown in **eFigures 8 and 9**.

The 6-minute walk test distance decreased from baseline to Week 52 in all treatment arms in ISABELA 1 and 2 (**eTable 6**).

5.7. All-cause mortality

Mortality rate (until end of study) was numerically higher with both doses of ziritaxestat versus placebo in ISABELA 2 and with ziritaxestat 200 mg versus placebo in ISABELA 1 (**Table 4**). Pooled data showed all-cause mortality was 8.9% and 7.0% with ziritaxestat 600 mg and 200 mg, respectively, versus 5.5% with placebo (HR [95% confidence interval]; 1.8 [1.1, 3.0] and 1.3 [0.8, 2.3], respectively; **Table 4**).

Respiratory-related deaths were the primary cause of mortality (adjudicated events that took place during the trials), occurring in 3.6%, 3.5% and 1.8% of patients in the ziritaxestat 600 mg, 200 mg and placebo groups, respectively, in ISABELA 1, and in 5.8%, 4.2% and 1.6% of patients in each group, respectively, in ISABELA 2 (**eTable 7**).

5.8. Treatment-emergent adverse events

In ISABELA 1, 78.7%, 84.6% and 84.5% of patients in the ziritaxestat 600 mg, 200 mg and placebo groups, respectively, had treatment-emergent adverse events (TEAEs); the corresponding data for ISABELA 2 were 81.1%, 85.8% and 75.6% (**Table 2**). Serious TEAEs occurred in 21.8%, 21.7% and 20.7% of patients in the ziritaxestat 600 mg, 200 mg and placebo groups, respectively, in ISABELA 1, and in 24.7%, 24.2% and 16.3% of these groups in ISABELA 2 (**Table 2**). TEAE data according to stratum are shown in **eTable 8** and TEAEs with a ≥5% incidence in at least one treatment group are listed in **eTable 9**; the most common TEAEs were gastrointestinal disorders.

TEAEs leading to death occurred in 4.6%, 3.4% and 4.6% of patients in the ziritaxestat 600 mg, 200 mg and placebo groups, respectively, in ISABELA 1, and 8.5%, 7.7% and 3.9% of these groups in ISABELA 2 (**Table 2**). IPF was the most common TEAE leading to death in the ziritaxestat 600 mg group in both ISABELA 1 and 2 (n=4 and n=5) while coronavirus disease 2019 (COVID-19) pneumonia and COVID-19 were the most common TEAEs leading to death in the ziritaxestat 200 mg group in ISABELA 1 and 2, respectively (n=2 and n=4) (**eTable 10**). The causes of death as provided by the investigator are listed in **eTable 11**. Overall, COVID-19–related TEAEs occurred in 3.8% of patients (**eTable 12**). Adjudicated deaths due to COVID-19 occurred in 0%, 1.8% and 0.6% of patients in the ziritaxestat 600 mg, ziritaxestat 200 mg and placebo groups, respectively, in ISABELA 1, and 0.8%, 1.9% and 0% of these groups, respectively, in ISABELA 2. The impact of COVID-19 on study visits is provided in **eTable 13**.

5.9. Pharmacokinetics and target engagement

Pharmacokinetic parameters of ziritaxestat are shown in **eTable 14**. A mixture model, which accounted for two responder sub-types, showed that in over 70% of the patients on active therapy, LPA level decreased from baseline (**eFigure 10)**. In the remaining, smaller cohort, there was an increase in LPA level post-treatment, not attributable to any difference in exposure to ziritaxestat.

6. Discussion

In the ISABELA studies, ziritaxestat did not lead to a reduction in the annual rate of FVC decline versus placebo; thus, the primary endpoint was not met. Ziritaxestat also failed to show benefit in secondary efficacy endpoints, such as time to first respiratory-related hospitalization, respiratory-related mortality, all-cause mortality or respiratory-related hospitalization, or acute IPF exacerbation, SGRQ total score or 6-minute walk test distance. All-cause mortality data showed a higher proportion of deaths with ziritaxestat 600 mg than placebo in ISABELA 1, and with each ziritaxestat dose than placebo in ISABELA 2.

Ziritaxestat did not reduce FVC decline compared with placebo, unlike in the prior phase 2a study,[16] although the latter included a limited number of patients. As in the phase 2a study, decreases in LPA were observed following ziritaxestat dosing; therefore, lack of target engagement is not considered the reason for the absence of effect on clinical endpoints. It is unknown why the positive results of the prior phase 2a study were not replicated in the ISBAELA studies, but the limitations associated with early phase trials such as small sample sizes, short duration and limited use of SoC therapies may be contributing factors. Lung function in patients on SoC was expected to decline at a slower rate than in untreated patients; however, this was not the case in the ISABELA studies. The extent of FVC decline in the ISABELA trials differed between strata and was greatest in patients taking pirfenidone. While suboptimal pirfenidone dosing was observed in some patients, it was not overly frequent, and is not thought to explain the apparent worsening of lung function. In addition, phase 1 data show ziritaxestat does not affect pirfenidone concentration. Therefore, the reason for this finding remains unclear.

Unlike for pirfenidone, phase 1 studies show ziritaxestat increases plasma levels of nintedanib. An increase in nintedanib levels could have led to the higher proportion of dose reductions, interruptions and non-diarrheal TEAEs observed with nintedanib versus pirfenidone in the ziritaxestat 600 mg group of the ISABELA trials. However, the dose of nintedanib administered has been shown to predict risk of diarrhea (which was the most frequent TEAE in the ziritaxestat 600 mg group), better than plasma exposure[20]. In the prior phase 2a study, ziritaxestat was administered as monotherapy and treatment with nintedanib was prohibited reducing the probability of dose reductions or treatment interruptions due to drug–drug interactions.

As stated, the IDMC's recommendation to terminate the studies was based on both lack of efficacy and a perceived increased mortality risk. Pooled data from ISABELA 1 and 2 showed an all-cause mortality rate of 8.9%, 7.0% and 5.5% with ziritaxestat 600 mg, ziritaxestat 200 mg and placebo, respectively, over a study duration of upwards of 100 weeks. A greater proportion of patient deaths occurred with ziritaxestat 600 mg than placebo in ISABELA 1, and with both ziritaxestat doses versus placebo in ISABELA 2. At the time of study termination, the number of patients enrolled and the number of patient-years of study drug exposure were greater in ISABELA 2 than ISABELA 1. Compared with ISABELA 1, there was a greater proportion of Asian patients in ISABELA 2. Whether this contributed to the greater proportion of deaths (including COVID-19–related deaths) in ISABELA 2 requires greater understanding of regional/racial differences in patients with IPF.

The COVID-19 pandemic, which arose after the studies were initiated, had some impact on study conduct and resulted in many clinic-based visits being missed by patients. Study safety was ensured by permitting telephone visits in place of scheduled clinic visits and performance of blood safety assessments in local laboratories. Fortunately, the proportion of COVID-19–related deaths was low, although where these occurred, they disproportionally affected the ziritaxestat treatment arms. A limited proportion of patients had missing spirometry data (1% had no post-baseline FVC data) , which arguably did not affect

analyses, and in addition, a mixed model for repeated measures was used, which mitigates the impact of some missing data.

Despite the regulatory requirement, testing new IPF medications on top of SoC is challenging as lung function in patients on currently available therapy is likely to decline at a slower rate than in untreated patients; however, as noted, this was not the case in the ISABELA trials. Furthermore, variability among individual patients may be amplified when testing a new therapy on top of local SoC, which can make data interpretation challenging. While the design of the ISABELA studies is not considered to have contributed to the negative findings, possible considerations for future IPF studies, which may increase the likelihood of identifying treatment effects, include the use of adaptive designs employing a Bayesian approach and biomarker-based enrichment strategies using prognostic biomarkers of early or more rapid disease progression.[21] Knowledge of patients' prior change in lung function would also allow better understanding of the rate of decline following the introduction of therapy. While the ISABELA studies failed, they demonstrate the potential value of observing data for ≥52 weeks and provide information regarding the utility of different clinical endpoints. In addition, information collected during studies, such as the faster than anticipated decline in FVC in the SoC strata, adverse events associated with SoC, and treatment patterns (e.g., the proportion of patients switching or initiating SoC during the trials), may help inform the design of future IPF studies.

Further investigation is needed to determine why the ISABELA trials failed. This may be determined by ongoing studies of other autotaxin inhibitors with different pharmacological characteristics to those of ziritaxestat (such as BBT-877[22]) or LPA receptor antagonists (such as BMS-986278[23]). Of note, the LPA receptor antagonist BMS-986020 was discontinued due to hepatobiliary toxicity; however, this was found to be unrelated to LPA antagonism[24,25] and, indeed, no such safety issues were identified in the ISABELA trials.

7. Limitations

The early termination of the studies is considered a possible limitation as it may have reduced our ability to adequately interpret the effect of treatment on the primary endpoint. Enrollment in ISABELA 1 was not complete so fewer patients entered the study than planned and outcomes beyond Week 52 were not captured for all patients. Another limitation is the missing data or visits due to the COVID-19 pandemic. The pandemic may also have influenced trial participation, and therefore the patient population may not reflect those in former IPF trials. In addition, the studies were not powered to assess true differences between strata (nintedanib vs pirfenidone vs no SoC).

8. Conclusion

The ISABELA studies did not demonstrate a benefit in their primary endpoint of annual rate of FVC decline, or in key secondary endpoints, compared with SoC in patients with IPF.

9. Acknowledgements

Author contributions

Toby M. Maher and Nadia Verbruggen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Toby M. Maher, Paul Ford, Kevin K Brown, Ann Fieuw, Wim A. Wuyts, Michael Kreuter, Marlies S. Wijsenbeek

Acquisition, analysis or interpretation of data: All authors

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis: Ineke Seghers and Nadia Verbruggen

Conflict of interest disclosures

Toby M. Maher, via his institution, has received industry-academic funding from Astra Zeneca and GlaxoSmithKline R&D; and consultancy or speaker fees from Astra Zeneca,

Bayer, Blade Therapeutics, Boehringer Ingelheim, BMS, CSL Behring, Fibrogen, Galapagos, Galecto, GlaxoSmithKline, IQVIA, Pliant, Roche, Trevi and Veracyte.

Paul Ford and **Niyati Prasad** are former employees of, and have received warrants from, Galapagos.

Kevin Brown reports support from the National Heart, Lung and Blood Institute; participation on a Scientific Advisory Board/work as an external science advisor for AbbVie, Blade Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, CSL Behring, DevPro Biopharma, Dispersol, Eleven P15, Galapagos, Galecto, Huitai Biomedicine, Open Source Imaging, Pliant, RedxPharma, Sanofi, Third Pole, and Translate Bio; participation on a data monitoring committee for Biogen and Humanetics, and work in a leadership or fiduciary role for the Fleischner Society and the Open Source Imaging Consortium (OSIC).

Ulrich Costabel reports personal fees from AstraZeneca, Boehringer Ingelheim, BMS, Fibrogen, Galapagos, Novartis, Pliant Therapeutics and Roche; and has served on data safety monitoring boards for Boehringer Ingelheim, Galapagos (including for the ISABELA studies), Roche and Sanofi.

Vincent Cottin reports unrestricted grant to institution from Boehringer Ingelheim; has served on data safety monitoring boards for Galapagos (including for the ISABELA studies), Galecto and Promedior/Roche; serves on adjudication committee for Fibrogen; and has received advisory board fees from Astra Zeneca, Boehringer Ingelheim, Celgene/BMS, CSL Behring, Galapagos, Pure Tech, RedX, Roche, Sanofi and Shionogi outside the submitted work.

Sonye K. Danoff via her institution, has received industry-academic funding from Boehringer Ingelheim, BMS and Genentech/Roche; fees related to clinical trials from Galecto; and advisory board fees from Boehringer Ingelheim outside the submitted work, as well as fees from Galapagos related to this trial.

Irene Groenveld, **Eric Helmer**, **Sanda Rocak** and **Ineke Seghers** are former employees of Galapagos.

Bernt Van Den Blink is a former employee and has received warrants from Galapagos.

R. Gisli Jenkins has received consulting fees from BMS, Chiesi, Daewoong, Pliant, Resolution Therapeutics and Veracyte; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or education events from AstraZeneca, Boehringer Ingelheim, Chiesi, PatientMPower and Roche; has participated on a data safety monitoring board or advisory board for Boehringer Ingelheim, Galapagos and Vicore; has held a leadership or fiduciary role in other board, society, committee or advocacy group for NuMedii; is a Trustee for Action for Pulmonary Fibrosis; and via his institution has received grants or contracts from AstraZeneca, Biogen, Galecto, GlaxoSmithKine, Nordic Biosciences, RedX and Pliant.

Julie Milner is a former employee of Gilead.

Geert Molenberghs, via his institution, has received academic-industry funding and speaker fees from Argenx, Boehringer, Galapagos, GlaxoSmithKline, Janssen Pharmaceutica, Sanofi, Regeneron, Roche, UCB.

Bjorn Penninckx is a consultant to Galapagos.

Matthew J. Randall, Ann Fieuw, Charlotte Vandenrijn and **Amit Taneja** are employees of, and have received warrants from, Galapagos.

Lixin Shao and **Timothy R. Watkins** are employees of Gilead.

Nadia Verbruggen is an employee of Galapagos.

Garrit Jentsch is a paid consultant for Galapagos.

Wim A. Wuyts reports no personal fees; the University Hospitals Leuven received grants and consultancy fees from Galapagos during the conduct of the study and grants from Boehringer Ingelheim and Roche outside the submitted work.

Michael Kreuter reports grants and personal fees from Galapagos during the conduct of the study, and grants and personal fees from Boehringer Ingelheim and Roche outside the submitted work.

Marlies S. Wijsenbeek-Lourens reports no personal fees; the Erasmus MC received consultancy or speaker fees from BMS, CSL Behring, Galapagos, Galecto, Horizon Therapeutics, Kinevant Sciences, Molecure, NeRRe Therapeutics, Novartis, PureTech Health, Respivant and Savara; and grants, speaker and consultancy fees from Boehringer Ingelheim and Hoffmann-La Roche outside the submitted work.

Funding: The ISABELA studies were funded by Galapagos NV (Mechelen, Belgium).

Role of the funder/sponsor: Galapagos was involved in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review and approval of the manuscript; and decision to submit the manuscript for publication.

Data sharing statement: Data will not be made available as informed consent was not obtained for the sharing of individual patient data.

Additional contributions

542 We thank all patients and investigators involved in the studies. A list of investigators who
543 randomized patients into each study is provided in the supplementary materials. We also
544 thank Simone Stutvoet, Luk Vandebriel and Lisa McCormick for their work on the study.

545 Medical writing support was provided by Debbie Sherwood, BSc, CMPP (Aspire Scientific
546 Ltd, Bollington, UK), and funded by Galapagos NV (Mechelen, Belgium).

547

10. References

1. Martinez FJ, Collard HR, Pardo A, et al. Idiopathic pulmonary fibrosis. *Nat Rev Dis Primers*. 2017;3:17074. doi:10.1038/nrdp.2017.74
2. Kreuter M, Swigris J, Pittrow D, et al. The clinical course of idiopathic pulmonary fibrosis and its association to quality of life over time: longitudinal data from the INSIGHTS-IPF registry. *Respir Res*. 2019;20(1):59. doi:10.1186/s12931-019-1020-3
3. Ley B, Collard HR, King TE, Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2011;183(4):431-440. doi:10.1164/rccm.201006-0894CI
4. Sharif R. Overview of idiopathic pulmonary fibrosis (IPF) and evidence-based guidelines. *Am J Manag Care*. 2017;23(11 Suppl):S176-S182.
5. Galli JA, Pandya A, Vega-Olivo M, Dass C, Zhao H, Criner GJ. Pirfenidone and nintedanib for pulmonary fibrosis in clinical practice: tolerability and adverse drug reactions. *Respirology*. 2017;22(6):1171-1178. doi:10.1111/resp.13024
6. Oikonomou N, Mouratis MA, Tzouvelekis A, et al. Pulmonary autotaxin expression contributes to the pathogenesis of pulmonary fibrosis. *Am J Respir Cell Mol Biol*. 2012;47(5):566-574. doi:10.1165/rcmb.2012-0004OC
7. Funke M, Zhao Z, Xu Y, Chun J, Tager AM. The lysophosphatidic acid receptor LPA1 promotes epithelial cell apoptosis after lung injury. *Am J Respir Cell Mol Biol*. 2012;46(3):355-364. doi:10.1165/rcmb.2010-0155OC
8. Sgalla G, Iovene B, Calvello M, Ori M, Varone F, Richeldi L. Idiopathic pulmonary fibrosis: pathogenesis and management. *Respir Res*. 2018;19(1):32. doi:10.1186/s12931-018-0730-2
9. Kraljic K, Jelic D, Ziher D, et al. Benzoxaboroles-novel autotaxin inhibitors. *Molecules*. 2019;24(19):3419. doi:10.3390/molecules24193419
10. Tager AM, LaCamera P, Shea BS, et al. The lysophosphatidic acid receptor LPA1 links pulmonary fibrosis to lung injury by mediating fibroblast recruitment and vascular leak. *Nat Med*. 2008;14(1):45-54. doi:10.1038/nm1685
11. Van Der Aar E, Fagard L, Desrivot J, et al. Favorable human safety, pharmacokinetics and pharmacodynamics of the autotaxin inhibitor GLPG1690, a potential new treatment in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2016;193:A2701.
12. Desroy N, Housseman C, Bock X, et al. Discovery of 2-[[2-Ethyl-6-[4-[2-(3-hydroxyazetidin-1-yl)-2-oxoethyl]piperazin-1-yl]-8-methyli midazo[1,2-a]pyridin-3-yl]methylamino]-4-(4-fluorophenyl)thiazole-5-carbonitrile (GLPG1690), a first-in-class autotaxin inhibitor undergoing clinical evaluation for the treatment of idiopathic pulmonary fibrosis. *J Med Chem*. 2017;60(9):3580-3590. doi:10.1021/acs.jmedchem.7b00032

13. Coornaert B, Duys I, Van Der Schueren J, Van Der Aar E, Heckmann B. Autotaxin inhibitor GLPG1690 affects TGFβ-induced production of the pro-fibrotic mediators CTGF, IL-6 and ET-1 in fibroblasts. *Am J Respir Crit Care Med*. 2017;195:A2404.
14. Ongenaert M, Dupont S, Blanqué R, Brys R, Van Der Aar E, Heckmann B. Strong reversal of the lung fibrosis disease signature by autotaxin inhibitor GLPG1690 in a mouse model for IPF. *Eur Respir J*. 2016;48:OA4540. doi:10.1183/13993003.congress-2016.OA4540
15. Heckmann B, Blanque R, Triballeau N, et al. Autotaxin inhibitors in IPF: elucidation of a novel binding mode for GLPG1690. *Am J Respir Crit Care Med*. 2019;199:A2585.
16. Maher TM, Van Der Aar EM, Van de Steen O, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of GLPG1690, a novel autotaxin inhibitor, to treat idiopathic pulmonary fibrosis (FLORA): a phase 2a randomised placebo-controlled trial. *Lancet Respir Med*. Aug 2018;6(8):627-635. doi:10.1016/S2213-2600(18)30181-4
17. Maher TM, Kreuter M, Lederer DJ, et al. Rationale, design and objectives of two phase III, randomised, placebo-controlled studies of GLPG1690, a novel autotaxin inhibitor, in idiopathic pulmonary fibrosis (ISABELA 1 and 2). *BMJ Open Respir Res*. 2019;6(1):e000422. doi:10.1136/bmjresp-2019-000422
18. Taneja A, Desrivot J, Diderichsen PM, et al. Population pharmacokinetic and pharmacodynamic analysis of GLPG1690, an autotaxin inhibitor, in healthy volunteers and patients with idiopathic pulmonary fibrosis. *Clin Pharmacokinet*. 2019;58(9):1175-1191. doi:10.1007/s40262-019-00755-3
19. Molenberghs GV, Verbeke, G. *Linear Mixed Models for Longitudinal Data*. Springer Series in Statistics Springer New York, NY; 2000.
20. Schmid U, Weber B, Sarr C, Freiwald M. Exposure-safety analyses of nintedanib in patients with chronic fibrosing interstitial lung disease. *BMC Pulm Med*. 2021;21(1):244. doi:10.1186/s12890-021-01598-0
21. Khan F, Stewart I, Howard L, et al. The Its Not JUST Idiopathic pulmonary fibrosis Study (INJUSTIS): description of the protocol for a multicentre prospective observational cohort study identifying biomarkers of progressive fibrotic lung disease. *BMJ Open Respir Res*. 2019;6(1):e000439. doi:10.1136/bmjresp-2019-000439
22. Lee G, Kang S, Ryou J-H, Lim J-J, Lee Y-H. BBT-877, a potent autotaxin inhibitor in clinical development to treat idiopathic pulmonary fibrosis. *Eur Respir J*. 2019;54:PA1293. doi:10.1183/13993003.congress-2019.PA1293
23. Corte TJ, Lancaster L, Swigris JJ, et al. Phase 2 trial design of BMS-986278, a lysophosphatidic acid receptor 1 (LPA1) antagonist, in patients with idiopathic pulmonary fibrosis (IPF) or progressive fibrotic interstitial lung disease (PF-ILD). *BMJ Open Respir Res*. 2021;8(1):e001026. doi:10.1136/bmjresp-2021-001026

24. Gill MW, Murphy BJ, Cheng PTW, Sivaraman L, Davis M, Lehman-McKeeman L. Mechanism of hepatobiliary toxicity of the LPA1 antagonist BMS-986020 developed to treat idiopathic pulmonary fibrosis: contrasts with BMS-986234 and BMS-986278. *Toxicol Appl Pharmacol*. 2022;438:115885. doi:10.1016/j.taap.2022.115885

25. Zulfikar S, Mulholland S, Adamali H, Barratt SL. Inhibitors of the autotaxin-lysophosphatidic acid axis and their potential in the treatment of interstitial lung disease: current perspectives. *Clin Pharmacol*. 2020;12:97-108. doi:10.2147/CPAA.S228362

26. Camarri B, Eastwood PR, Cecins NM, Thompson PJ, Jenkins S. Six minute walk distance in healthy subjects aged 55-75 years. *Respir Med*. Apr 2006;100(4):658-65. doi:10.1016/j.rmed.2005.08.003

10. Tables

Table 1. Baseline demographics, disease characteristics and stratum

	ISABELA 1			ISABELA 2		
	Ziritaxestat 600 mg (n=174)	**Ziritaxestat 200 mg (n=175)**	**Placebo (n=174)**	**Ziritaxestat 600 mg (n=259)**	**Ziritaxestat 200 mg (n=260)**	**Placebo (n=258)**
Age, years	69.4 (7.2)	70.0 (6.7)	70.6 (7.7)	69.2 (7.2)	69.7 (7.3)	70.6 (6.6)
Male, n (%)	142 (81.6)	143 (81.7)	146 (83.9)	209 (80.7)	213 (81.9)	209 (81.0)
Female, n (%)	32 (18.4)	32 (18.3)	28 (16.1)	50 (19.3)	47 (18.1)	49 (19.0)
Race, n (%)						
American Indian or Alaska native	10 (5.7)	6 (3.4)	6 (3.4)	2/251 (0.8)	1/252 (0.4)	2/252 (0.8)
Asian	11 (6.3)	9 (5.1)	9 (5.2)	72/251 (28.7)	72/252 (28.6)	68/252 (27.0)
Black or African American	1 (0.6)	0	0	2/251 (0.8)	0/252 (0.0)	1/252 (0.4)
Multiple	0	0	0	0/251 (0.0)	1/252 (0.4)	2/252 (0.8)
Native Hawaiian or Other Pacific Islander	0	0	0	1/251 (0.4)	0/252 (0.0)	1/252 (0.4)
White	152 (87.4)	160 (91.4)	159 (91.4)	174 (69.3)	178/252 (70.6)	178/252 (70.6)
Geographical region, n (%)						
Asia-Pacific	24 (13.8)	29 (16.6)	22 (12.6)	67 (25.9)	76 (29.2)	71 (27.5)
EMEA	73 (42.0)	70 (40.0)	77 (44.3)	100 (38.6)	90 (34.6)	86 (33.3)
Latin America	35 (20.1)	21 (12.0)	22 (12.6)	30 (11.6)	33 (12.7)	27 (10.5)
Northern America	42 (24.1)	55 (31.4)	53 (30.5)	62 (23.9)	61 (23.5)	74 (28.7)
Former smoker, n (%)	99 (56.9)	110 (62.9)	113 (64.9)	177 (68.3)	195 (75.0)	183 (70.9)
Current smoker, n (%)	5 (2.9)	2 (1.1)	0	5 (1.9)	2 (0.8)	5 (1.9)
BMI, kg/m^2	27.6 (4.0)	28.3 (3.9)	27.9 (3.8)	26.7 (3.9)	27.3 (3.7)	27.1 (4.3)
Oxygen saturation at rest, %	95.8 (2.1)	95.8 (2.0)	95.7 (1.9)	95.6 (2.2)	95.5 (2.0)	95.7 (2.1)

Receiving oxygen at rest, n (%)	11 (6.3)	7 (4.0)	9 (5.2)	16 (6.2)	10 (3.8)	13 (5.0)
Duration of IPF, years	2.3 (1.4)	2.3 (1.4) [174]	2.3 (1.4)	2.2 (1.5)	2.3 (1.5)	2.2 (1.5) [257]
Duration of IPF, years, median (min, max) [n]	2.1 (0.1, 5.8)	2.1 (0.1, 5.5) [174]	2.0 (0.1, 6.6)	2.0 (0.1, 11.8)	2.1 (0.1, 6.3)	1.9 (0.1, 5.8) [257]
FVC, mL	2947.0 (820.8)	2873.2 (815.8)	2943.3 (738.7)	2775.7 (823.2)	2768.6 (701.9)	2749.5 (785.1) [256]
Percent predicted FVC,[a] %	80.4 (17.5)	77.9 (18.1)	79.7 (15.9)	76.5 (16.8)	77.7 (15.5)	77.6 (17.2) [256]
FEV_1/FVC ratio, %	82.0 (5.9)	82.4 (5.6)	82.3 (4.7)	82.9 (5.8)	82.8 (5.7)	82.7 (6.0) [256]
SGRQ total score,[b] %	34.1 (18.5) [173]	35.9 (19.1)	35.2 (17.9) [173]	36.9 (20.2) [258]	36.6 (20.3) [258]	34.9 (19.2) [257]
6MWT distance,[c] m	416.3 (101.6) [173]	403.7 (105.1)	400.8 (119.1)	408.3 (110.9)	395.7 (133.9) [257]	400.4 (105.4) [257]
Percent predicted DLCO corrected for hemoglobin, %	56.4 (18.9)	54.0 (16.3)	53.1 (16.3)	54.3 (19.6) [258]	53.1 (17.5) [259]	57.1 (21.7) [257]
Concomitant use of proton pump inhibitors	91 (52.3)	90 (51.4)	86 (49.4)	133 (51.4)	131 (50.4)	139 (53.9)
Stratum, n (%)						
Pirfenidone[d]	69 (39.7)	70 (40.0)	69 (39.7)	84 (32.4)	85 (32.7)	83 (32.2)
Nintedanib[d]	60 (34.5)	61 (34.9)	60 (34.5)	89 (34.4)	91 (35.0)	91 (35.3)
Neither	45 (25.9)	44 (25.1)	45 (25.9)	86 (33.2)	84 (32.3)	84 (32.6)

[a]Predicted FVC calculated using the 2012 Global Lung Function Initiative Equations.
[b]SGRQ is a 50-item health-related quality of life patient questionnaire with domains covering respiratory symptoms, activity levels, and psychosocial impact. Scores range from 0-100, with a higher score indicating poorer health-related quality of life.
[c]Average 6MWT distance in healthy subjects aged 55–75 years is 659 metres.
[d]See **eTable 3** for doses of standard of care medication[26].
Values are mean (SD) [n] unless otherwise stated. Full analysis set.
6MWT, 6-minute walk test; BMI, body mass index; DLCO, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; SD, standard deviation; SGRQ, St George Respiratory Questionnaire.

Table 2. Treatment-emergent adverse events and dose reductions/interruptions/discontinuations

	ISABELA 1			ISABELA 2		
Patients, n (%)	**Ziritaxestat 600 mg (n=174)**	**Ziritaxestat 200 mg (n=174)**	**Placebo (n=174)**	**Ziritaxestat 600 mg (n=259)**	**Ziritaxestat 200 mg (n=260)**	**Placebo (n=258)**
TEAE	137 (78.7)	148 (84.6)	147 (84.5)	210 (81.1)	223 (85.8)	195 (75.6)
Serious TEAE	38 (21.8)	38 (21.7)	36 (20.7)	64 (24.7)	63 (24.2)	42 (16.3)
Death	8 (4.6)	6 (3.4)	8 (4.6)	22 (8.5)	20 (7.7)	10 (3.9)
Worst TEAE severity						
Death	9 (5.2)	6 (3.4)	8 (4.6)	22 (8.5)	20 (7.7)	10 (3.9)
Life-threatening	3 (1.7)	5 (2.9)	4 (2.3)	5 (1.9)	1 (0.4)	4 (1.6)
Severe	29 (16.7)	35 (20.0)	26 (14.9)	38 (14.7)	44 (16.9)	33 (12.8)
Moderate	82 (47.1)	69 (39.4)	80 (46.0)	111 (42.9)	108 (41.5)	108 (41.9)
Mild	14 (8.0)	33 (18.9)	29 (16.7)	34 (13.1)	50 (19.2)	40 (15.5)
Treatment-related TEAE to study drug	60 (34.5)	53 (30.3)	53 (30.5)	96 (37.1)	80 (30.8)	70 (27.1)
Treatment-related TEAE to pirfenidone	22 (12.6)	28 (16.0)	26 (14.9)	19 (7.3)	34 (13.1)	30 (11.6)
Treatment-related TEAE to nintedanib	50 (28.7)	39 (22.3)	26 (14.9)	80 (30.9)	54 (20.8)	42 (16.3)
Dose reductions/interruptions/discontinuations						
Study drug:						
Permanently stopped	18 (10.3)	10 (5.7)	13 (7.5)	29 (11.2)	27 (10.4)	18 (7.0)
Interrupted	30 (17.2)	29 (16.6)	23 (13.2)	57 (22.0)	37 (14.2)	33 (12.8)
Reduced	9 (5.2)	6 (3.4)	3 (1.7)	30 (11.6)	12 (4.6)	9 (3.5)
Pirfenidone:						
Permanently stopped	3 (1.7)	2 (1.1)	4 (2.3)	8 (3.1)	3 (1.2)	8 (3.1)
Interrupted	4 (2.3)	4 (2.3)	5 (2.9)	8 (3.1)	9 (3.5)	5 (1.9)
Reduced	1 (0.6)	3 (1.7)	3 (1.7)	5 (1.9)	6 (2.3)	2 (0.8)
Nintedanib:						
Permanently stopped	4 (2.3)	6 (3.4)	0	10 (3.9)	3 (1.2)	2 (0.8)
Interrupted	13 (7.5)	10 (5.7)	10 (5.7)	25 (9.7)	19 (7.3)	14 (5.4)
Reduced	7 (4.0)	3 (1.7)	6 (3.4)	24 (9.3)	8 (3.1)	10 (3.9)

Full analysis set. Events listed in table occurred during the trial, on or after the start of study drug intake and within 30 days after the last dose of study drug until the end of the study.
TEAE, treatment-emergent adverse event.

Table 3. Annual rate of FVC decline up to Week 52 and until end of study

	Ziritaxestat 600 mg	Ziritaxestat 200 mg	Placebo	Difference between ziritaxestat 600 mg and placebo[a]	Difference between ziritaxestat 200 mg and placebo[a]
Annual rate of FVC decline up to Week 52					
ISABELA 1 LS mean (95% CI) [n]	−124.6 (−178.0, −71.2) [174]	−173.9 (−225.7, −122.2) [175]	−147.3 (−199.8, −94.7) [174]	22.7 (−52.3, 97.6)	−26.7 (−100.5, 47.1)
ISABELA 2 LS mean (95% CI) [n]	−173.8 (−209.2, −138.4) [259]	−174.9 (−209.5, −140.2) [260]	−176.6 (−211.4, −141.8) [258]	2.8 (−46.9, 52.4)	1.7 (−47.4, 50.8)
ISABELA 1 and 2 (pooled) LS mean (95% CI) [n]	−156.5 (−186.2, −126.7) [428]	−173.7 (−202.7, −144.7) [431]	−165.7 (−194.9, −136.4) [422]	9.2 (−32.5, 50.9)	−8.0 (−49.2, 33.1)
Annual rate of FVC decline until end of study (ISABELA 1 and 2 pooled)					
All strata LS mean (95% CI) [n]	−161.0 (−187.4, −134.5) [428]	−174.4 (−200.0, −148.7) [431]	−169.0 (−195.0, −143.0) [422]	8.0 (−29.0, 45.1)	−5.4 (−41.9, 31.1)
Pirfenidone LS mean (95% CI) [n]	−194.3 (−238.2, −150.3) [151]	−217.9 (−259.5, −176.3) [154]	−189.0 (−231.6, −146.3) [149]	−5.3 (−66.6, 56.0)	−29.0 (−88.6, 30.6)
Nintedanib LS mean (95% CI) [n]	−132.4 (−176.2, −88.6) [146]	−132.2 (−175.2, −89.2) [151]	−163.1 (−205.7, −120.5) [147]	30.7 (−30.4, 91.9)	30.9 (−29.7, 91.5)
Neither LS mean (95% CI) [n]	−155.1 (−204.8, −105.3) [131]	−168.4 (−217.5, −119.3) [126]	−149.1 (−199.5, −98.6) [126]	−6.0 (−76.9, 64.9)	−19.3 (−89.7, 51.1)

[a]Positive difference in values indicates that patients receiving ziritaxestat deteriorate less than those receiving placebo.
Full analysis set.
CI, confidence interval; FVC, forced vital capacity; LS, least squares; SE, standard error.

Table 4. Risk of all-cause mortality with ziritaxestat versus placebo (until the end of the studies)

	Ziritaxestat 600 mg (N=428)		Ziritaxestat 200 mg (N=431)		Placebo (N=422)		Ziritaxestat 600 mg versus placebo		Ziritaxestat 200 mg versus placebo	
	Events n (%)	**Incidence rate per 100 PYE**	**Events n (%)**	**Incidence rate per 100 PYE**	**Events n (%)**	**Incidence rate per 100 PYE**	**Difference in incidence rate (CI)**	**HR (CI)**	**Difference in incidence rate (CI)**	**HR (CI)**
ISABELA 1	14 (8.0)	8.1	8 (4.6)	4.3	11 (6.3)	6.3	1.8 (-4.3, 8.0)	1.4 (0.6, 3.1)	-1.9 (-7.5, 3.6)	0.7 (0.3, 1.8)
ISABELA 2	24 (9.3)	8.9	22 (8.5)	8.1	12 (4.7)	4.4	4.5 (0.0, 9.1)	2.1 (1.1, 4.3)	3.7 (-0.7, 8.1)	1.9 (0.9, 3.8)
ISABELA 1 and 2 pooled	38 (8.9)	8.6	30 (7.0)	6.6	23 (5.5)	5.1	3.5 (-0.1, 7.1)	1.8 (1.1, 3.0)	1.5 (-1.9, 4.8)	1.3 (0.8, 2.3)

Full-analysis set.
CI, confidence interval; HR, hazard ratio; IR, incidence rate; PYE, patient years of exposure.

11. Figure legends

Figure 1. Patient disposition in ISABELA 1 (a) and ISABELA 2 (b)

At the time of study termination, enrollment was ongoing in ISABELA 1 and had completed in ISABELA 2. The discrepancy between the number of deaths reported here for patient disposition and in the results is because of incomplete data cleaning due to the early termination of the studies; the total number of deaths was ziritaxestat 600 mg: 14, ziritaxestat 200 mg: 8, placebo: 11 in ISABELA 1 and ziritaxestat 600 mg: 24, ziritaxestat 200 mg: 22, placebo: 12 in ISABELA 2.

* FVC ≥45% predicted of normal, FEV_1/FVC ≥0.7 and DLCO corrected for hemoglobin ≥30% predicted of normal.

DLCO, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; HRCT, high-resolution computed tomography