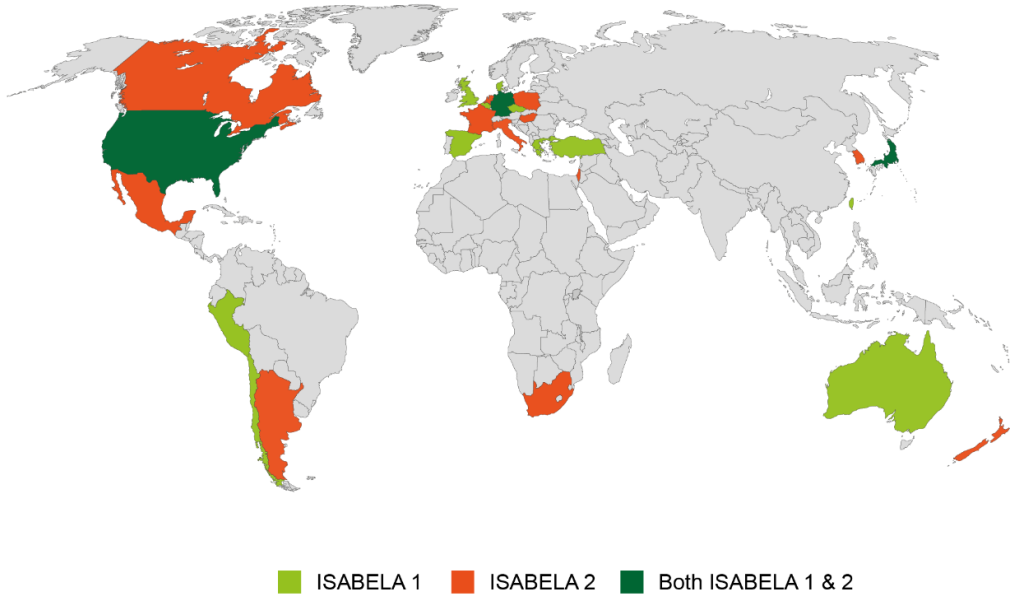
Supplemental Online Content

Maher TM, Ford P, Brown KK, et al; for the ISABELA 1 and 2 investigators. Ziritaxestat, a novel autotaxin inhibitor, and lung function in idiopathic pulmonary fibrosis: the ISABELA 1 and 2 randomized clinical trials. *JAMA*. Published May 9, 2023. doi:10.1001/jama.2023.5355

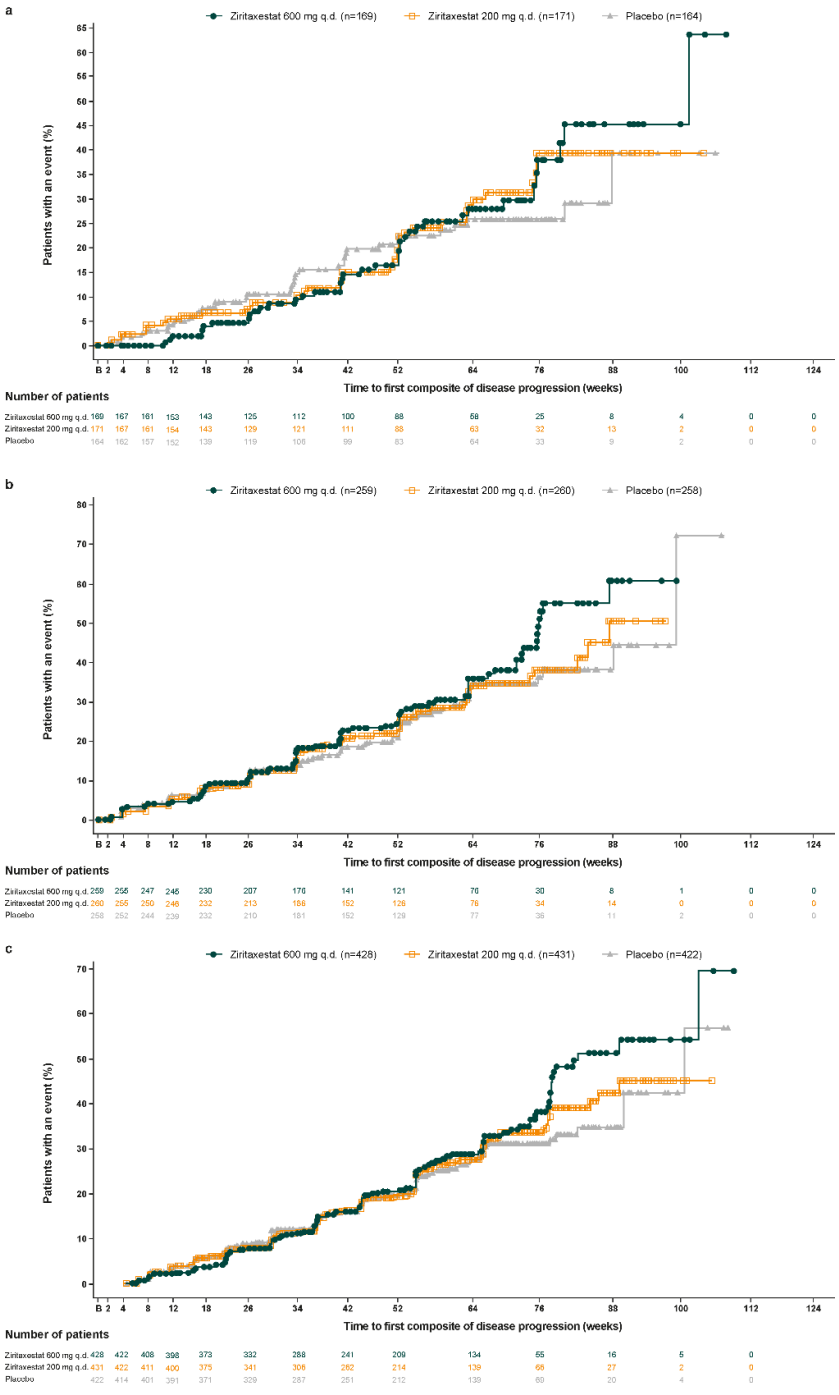
This supplemental material has been provided by the authors to give readers additional information about their work.

eFigure 1. Number of patients in each country participating in ISABELA 1 and 2

	Number of patients	
	ISABELA 1	ISABELA 2
Asia-Pacific		
Australia	51	0
Japan	3	121
Korea (Republic of)	0	76
New Zealand	0	17
Taiwan	21	0
Total	**75**	**214**
EMEA		
Belgium	27	0
Czech Republic	16	0
Denmark	28	0
France	0	21
Germany	41	33
Greece	15	0
Hungary	0	12
Israel	0	64
Italy	0	31
Netherlands	0	64
Poland	0	31
South Africa	0	20
Spain	39	0
Turkey	24	0
United Kingdom	30	0
Total	**220**	**276**
Latin America		
Argentina	0	59
Chile	57	0
Mexico	0	31
Peru	21	0
Total	**78**	**90**
Northern America		
Canada	0	32
United States	150	165
Total	**150**	**197**

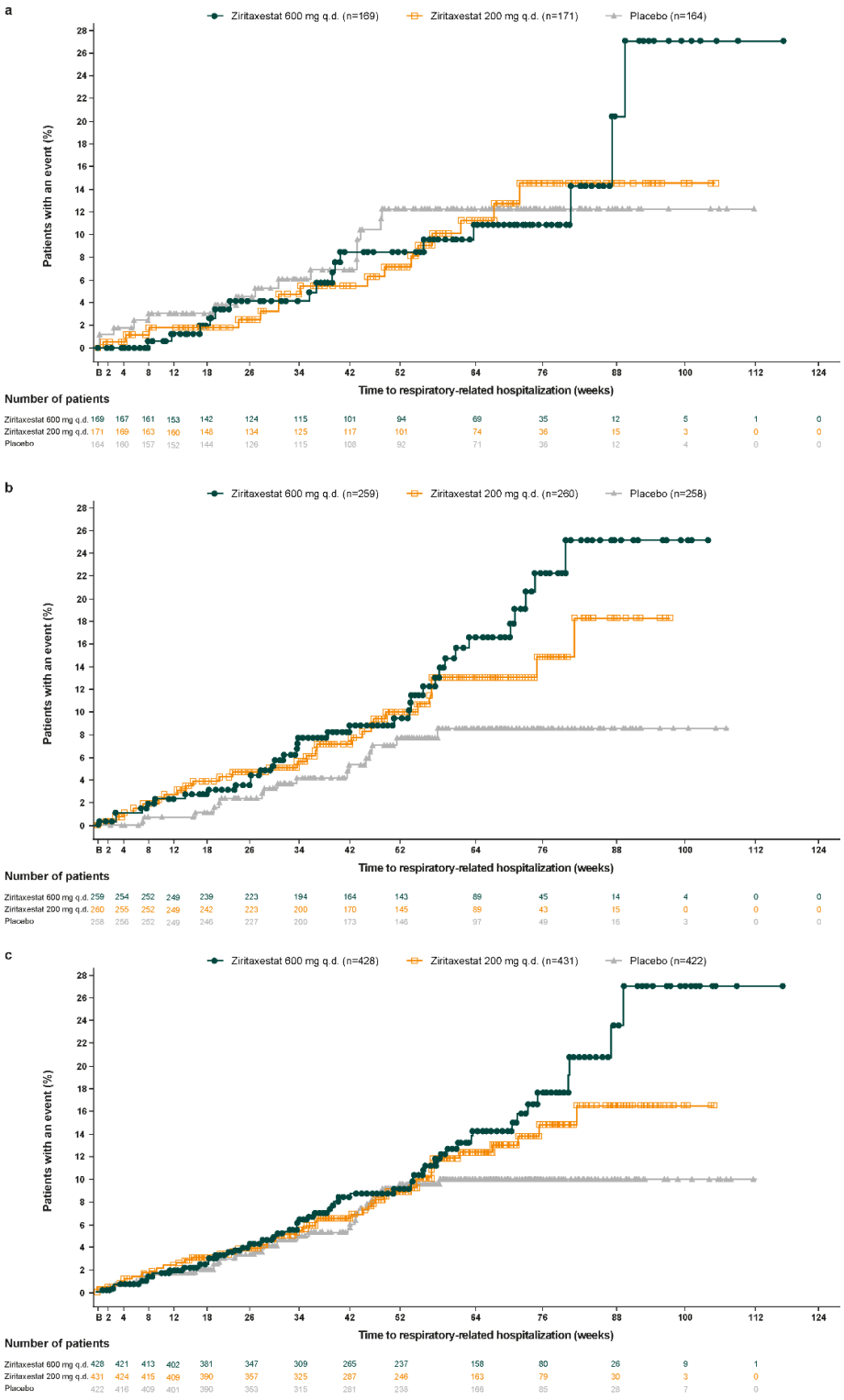


eFigure 2. Time to disease progression (composite endpoint of first occurrence of ≥10% absolute decline in percent predicted FVC or all-cause mortality) in ISABELA 1 (a), ISABELA 2 (b) and ISABELA 1 and 2 combined (c)



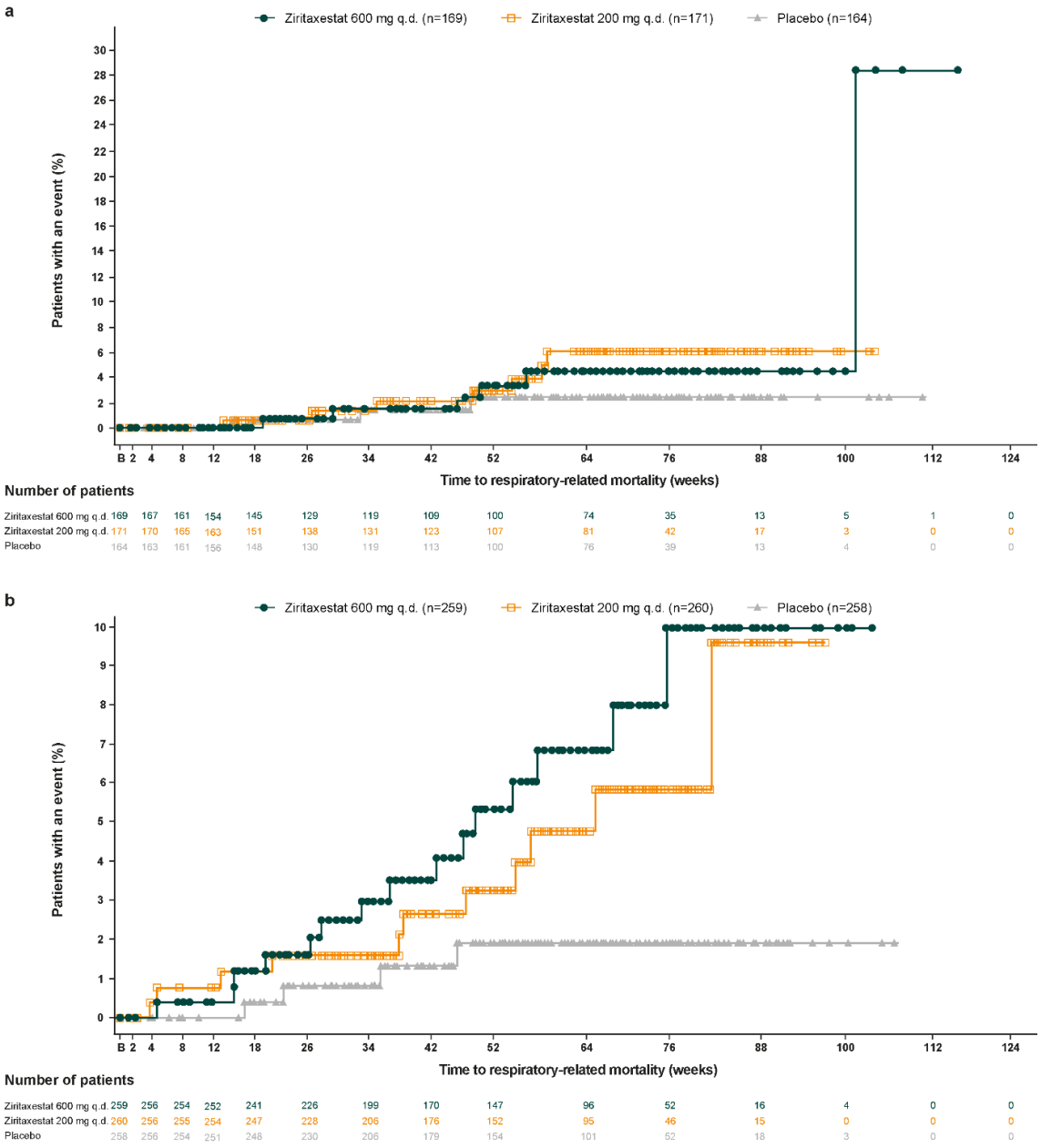
Full analysis set.
Disease progression: composite endpoint of first occurrence of ≥10% absolute decline in percent predicted FVC or all-cause mortality at Week 52.
B, baseline; FVC, forced vital capacity; q.d., once daily.

eFigure 3. Time to first adjudicated respiratory-related hospitalization for ISABELA 1 (a), ISABELA 2 (b) and ISABELA 1 and 2 combined (c)



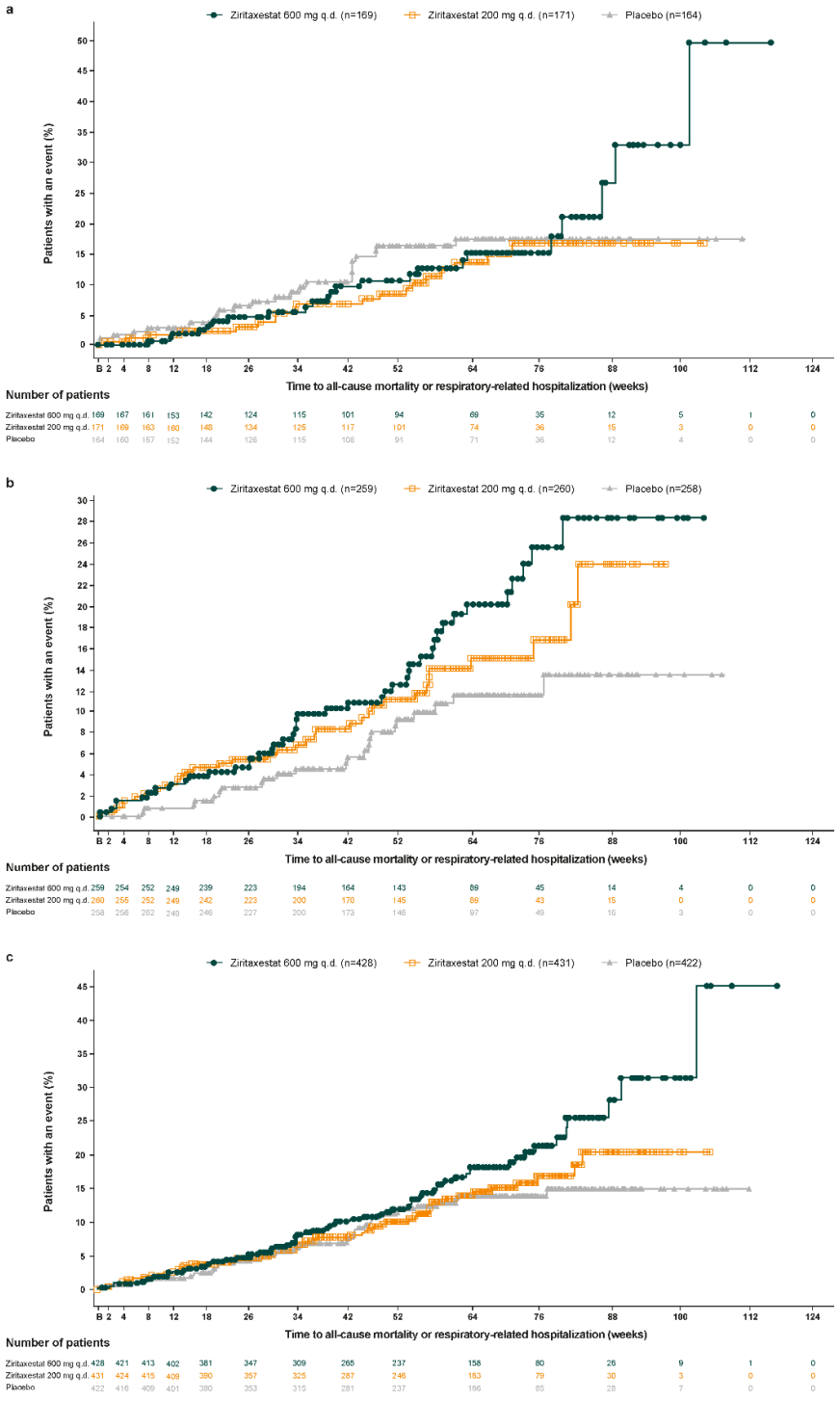
Full analysis set.
B, baseline; q.d., once daily.

eFigure 4. Time to respiratory-related mortality in ISABELA 1 (a) and ISABELA 2 (b) (adjudicated)



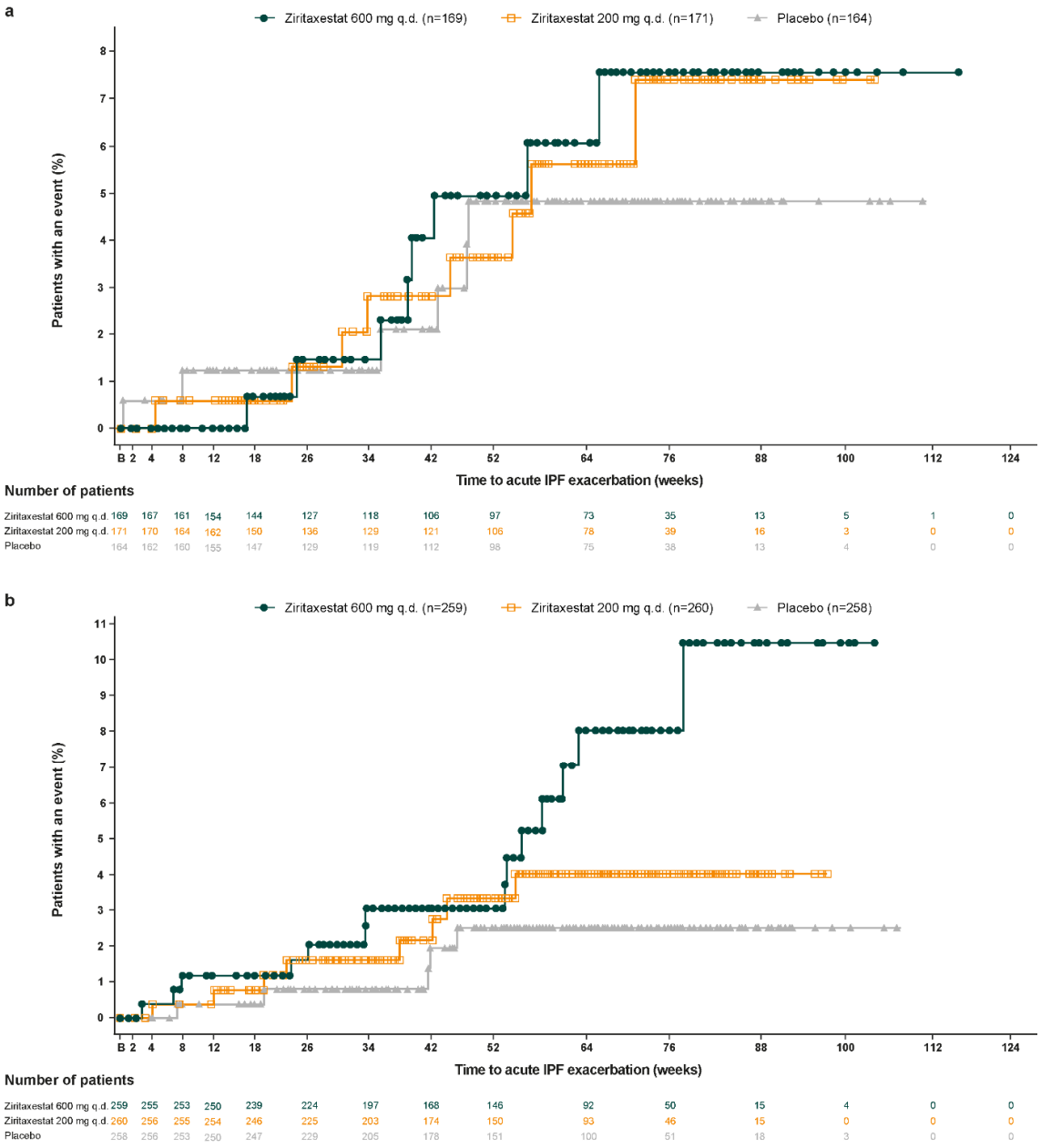
Full analysis set.
B, baseline; q.d., once daily.

eFigure 5. Time to all-cause mortality or respiratory-related hospitalization (adjudicated) for ISABELA 1 (a), ISABELA 2 (b) and ISABELA 1 and 2 combined (c)



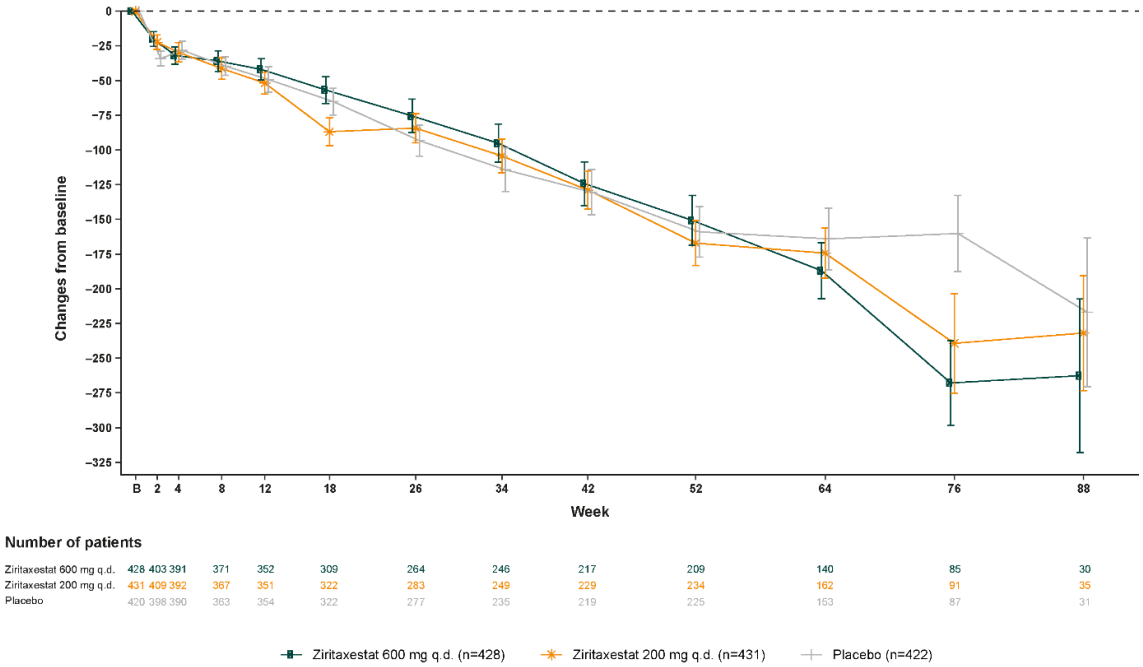
Full analysis set.
B, baseline; q.d., once daily.

eFigure 6. Time to first acute IPF exacerbation (adjudicated) in ISABELA 1 (a) and ISABELA 2 (b)



Full analysis set.
B, baseline; IPF, idiopathic pulmonary fibrosis; q.d., once daily.

eFigure 7. Mean change from baseline in FVC over time for ISABELA 1 and 2 combined



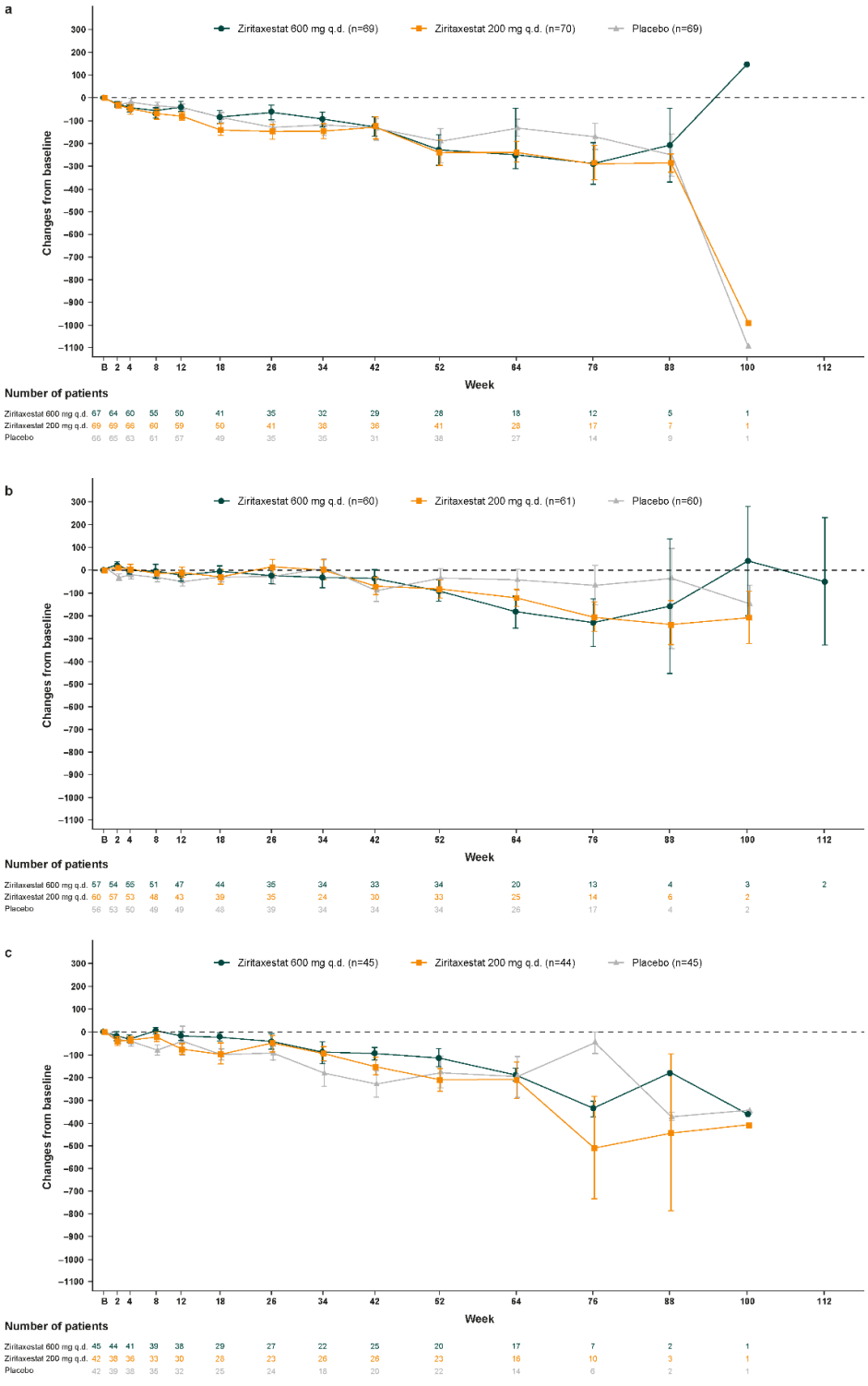
Number of patients

Ziritaxestat 600 mg q.d.	428	403	391	371	352	309	264	246	217	209	140	85	30
Ziritaxestat 200 mg q.d.	431	409	392	367	351	322	283	249	229	234	162	91	35
Placebo	420	398	390	363	354	322	277	235	219	225	163	87	31

Ziritaxestat 600 mg q.d. (n=428) Ziritaxestat 200 mg q.d. (n=431) Placebo (n=422)

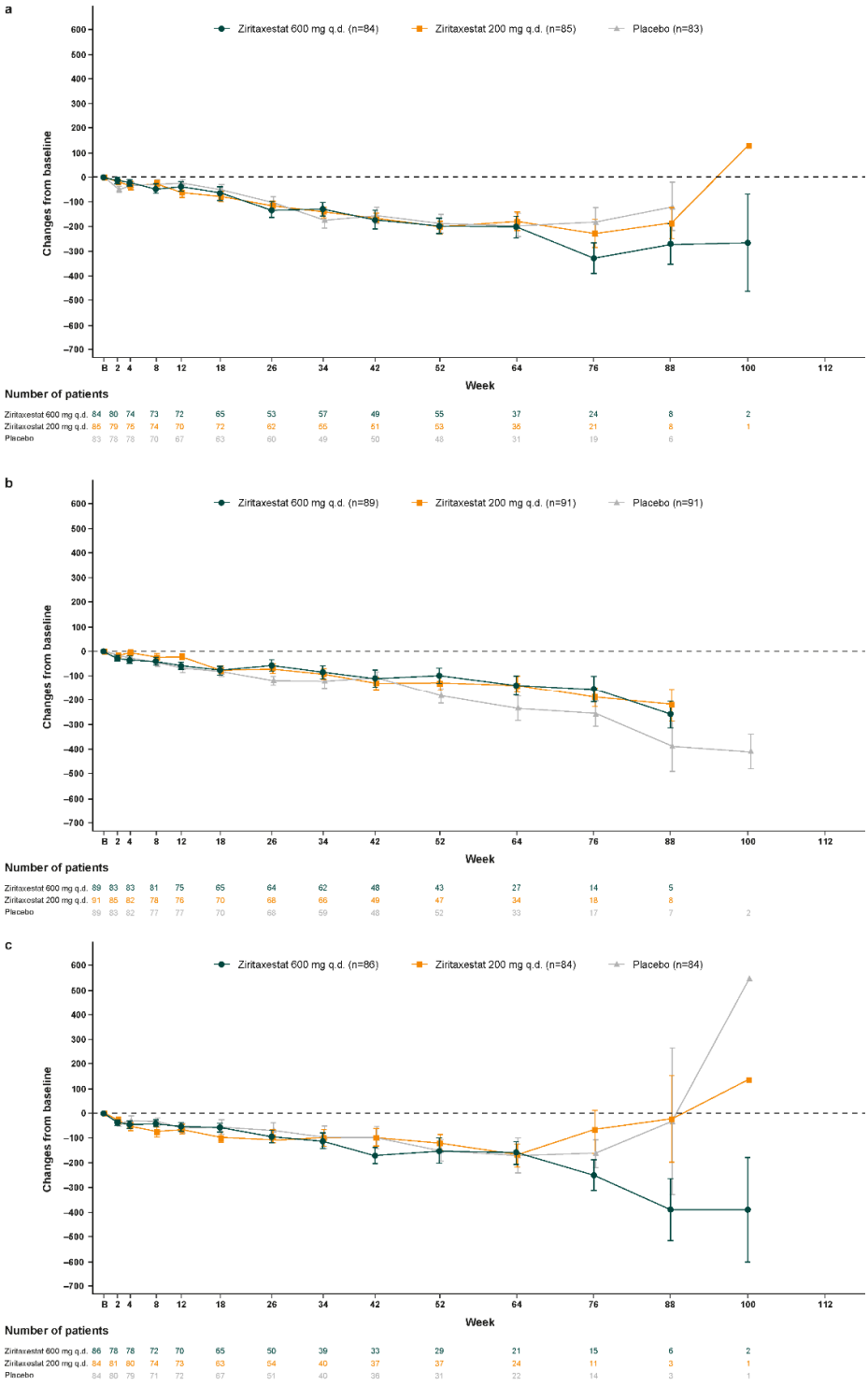
Full analysis set.
B, baseline; FVC, forced vital capacity; q.d., once daily.

eFigure 8. Change from baseline in FVC in the pirfenidone (a), nintedanib (b) and neither (c) stratum of ISABELA 1



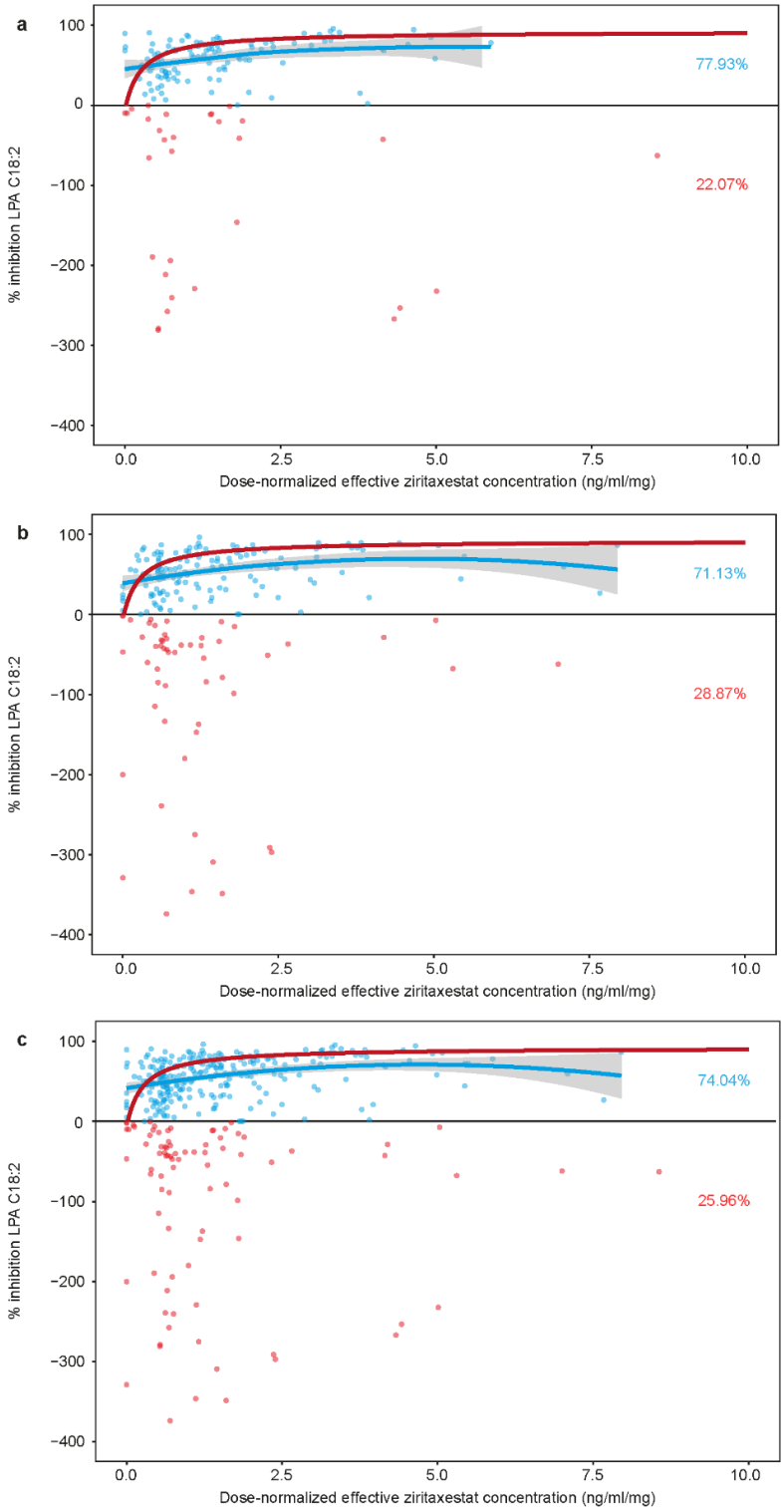
B, baseline; q.d., once daily.

eFigure 9. Change from baseline in FVC in the pirfenidone (a), nintedanib (b) and neither (c) stratum of ISABELA 2



B, baseline; q.d., once daily.

eFigure 10. Two responder phenotypes in the population of ISABELA 1 (a), ISABELA 2 (b) and ISABELA 1 and 2 combined (c)



The red curve depicts the theoretical exposure–response predicted based on the model developed predominantly from data from healthy volunteers. The blue curve is the observed exposure–response trend line in responders. The percentages and circles indicate the percentage of observations with an inhibition of LPA post-dose (blue circles indicate responders, ie those with post-dose inhibition of LPA) vs those with a post dose increase in LPA (red circles indicate non-responders ie, those with post-dose increase in LPA).
LPA, lysophosphatidic acid.

eMethods

Endpoints

Secondary endpoints included time to respiratory-related mortality until the end of the study; time to all-cause mortality or respiratory-related hospitalization until the end of the study; time to first acute idiopathic pulmonary fibrosis (IPF) exacerbation until the end of the study; change from baseline in forced vital capacity (FVC) at Week 52 and end of the study; change from baseline in the 6-minute walk test distance at 52 weeks and until the end of the study. Other endpoints included changes over time in target engagement/pharmacodynamics.

All-cause mortality included all deaths reported during the study and deaths that could be determined via vital status forms (vital status information was collected at Week 52, at the end of the study or at early discontinuation, and at the follow-up visit). Treatment-emergent adverse events were defined as any adverse event (AE) with an onset date on or after the start of study drug intake and no later than 30 days after last dose of study drug, or any worsening of any AE on or after the start of study drug intake.

Randomization and blinding

Each patient was allocated to a given treatment using a centralized electronic system (interactive web response system [IWRS]) with permuted blocks. Allocation was described in a randomization list prepared by a contract research organization, which was stratified in a balanced manner for background SoC. For each patient, at each visit the clinical study center contacted the IWRS for the appropriate treatment number to be assigned. Patients and study personnel were blinded to the assigned treatment and blinded medication was provided to the clinical study center.

Pharmacokinetic assessments

Pharmacokinetic assessments included the plasma concentration of ziritaxestat, pirfenidone and nintedanib, measured using a validated liquid chromatography with tandem mass spectrometry (LC-MS). Blood samples were collected before study drug, pirfenidone or nintedanib intake, then at Visit 3, 9 and 12. At Visit 7 and 10, samples were collected before study drug intake, but after pirfenidone or nintedanib intake, and 2 to 3 hours after study drug intake. Thereafter, samples were taken every 24 weeks before study drug intake, but after pirfenidone or nintedanib intake. Non-linear mixed effects models were applied to the data to describe the time course of ziritaxestat in the plasma and subsequently describe its exposure–response relationship. The published model [1] was taken as the base model, with effect of standard of care (SoC) and acid-reducing agents on ziritaxestat exposure evaluated as categorical covariates. Given the sparse dataset, the population pharmacokinetics model of ziritaxestat was simplified to a one-compartment model with first-order absorption. Model-based pharmacokinetic parameters (maximum observed plasma concentration at steady state [C_{max}], minimum [trough] observed plasma concentration [C_{min}] and area under the plasma concentration–time curve at steady state [AUC_{ss}]) were subsequently computed.

Pharmacodynamic assessments

Target engagement (autotaxin inhibition) was measured by determination of lysophosphatidic acid (LPA) C18:2 in the plasma using LC-MS. LPA levels were measured at C_{trough} at baseline, Week 26 and Week 52. Due to the limited number of samples that could be analyzed in the available timeframe, LPA was measured in a random subset of patients with an equal distribution over the treatment subgroups. The exposure–response relationship was described by fitting a population pharmacokinetic–pharmacodynamic model to the data, which aimed to evaluate target engagement across treatment strata and determine whether differences, if any, were attributable to differences in exposure. A mixture model was developed, which accounted for two responder sub-types. The structural model used to describe these patients was similar to that described previously by Taneja et al [1], i.e., the observed plasma LPA C18:2 was described by an I_{max} function driven from an effective ziritaxestat concentration, defined as the weighted sum of the ziritaxestat plasma concentration and a hypothetical effect-site concentration.

Model evaluation was performed by applying standard statistical and visual diagnostic criteria [2].

Statistical analyses

Dose records describing ziritaxestat dosing amounts and administration times, covariates accounting for the SoC and acid-reducing agents, and measured ziritaxestat plasma concentrations were merged and formatted as a NONMEM-compatible analysis dataset using the R programming language (version 3.6.0 or higher). Similarly, a NONMEM-compatible analysis dataset was created for the modelling of LPA C18:2 plasma concentrations.

To analyze the pharmacokinetics and pharmacodynamics of ziritaxestat, non-linear mixed-effect modelling was performed using NONMEM (ICON Development Solutions, version 7.4.3). Analysis of results and simulations were performed using R (version 3.6.9 or higher).

Investigators who randomized patients to the studies

ISABELA 1

Australia: Daniel Chambers, Michael Chia, Tamera Corte, Ian Glaspole, Nicole Goh, Mark Holmes, Monique Malouf, Francis Thien, Elizabeth Veitch
Belgium: Benjamin Bondue, Caroline Dahlqvist, Antoine Froidure, Hans Slabbynck, Wim Wuyts
Chile: Claudia Cartagena Salinas, Rosa Feijoó Seoane, Victor Martínez, Roxana Maturana, Juana Pavie Gallegos, Andres Rosenblut, Rafael Silva, Alvaro Undurraga Pereira
Czech Republic: Martina Doubkova, Norbert Pauk, Martina Plackova, Martina Sterclova
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Greece: Katerina Antoniou, Zoe Daniil, Mina Gaga, Despoina Papakosta
Japan: Shinyu Izumi, Masaki Okamoto
Peru: Alfredo Guerreros Benavides, Carlos Iberico Barrera, Alejandro Manuel Peña Villalobos
Spain: Aranzazu Campo Ezquibela, Jose Manuel Cifrian Martinez, Estrella Fernandez Fabrellas, Virginia Leiro, Maria Molina-Molina, Asunción Nieto Barbero, Jacobo Sellares Torres, Claudia Valenzuela
Taiwan: Shih-Lung Cheng, Ping-Hung Kuo, Kang-Yun Lee, Chau-Chyun Sheu
Turkey: Hakan Gunen, Nesrin Mogulkoc Bishop, Sibel Nayci
United Kingdom: Huzaifa Adamali, Stephen Bianchi, Nazia Chaudhuri, Michael Gibbons, Simon Hart, Philip Molyneaux, Helen Parfrey, Gauri Saini, Lisa G Spencer, Sarah Wiscombe
United States: Danielle Antin-Ozerkis, Rebecca Bascom, John Belperio, Edward Britt, John Fitzgerald, Diana Gomez Manjarres, Mark Gotfried, Nishant Gupta, David Hotchkin, Mitchell Kaye, Mary Kreider, Shahrukh Kureishy, Peter Lacamera, Lisa Lancaster, Joseph Lasky, Daniel Lorch, Hannah Mannem, Lee Morrow, Teng Moua, Anoop Nambiar, Ganesh Raghu, Rishi Raj, Murali Ramaswamy, Raghu Reddy, Tonya Russell, Mary Beth Scholand, Barry Shea, Sally Suliman, Jeff Swigris, Krishna Thavarajah, Leslie Tolle, Rade Tomic, Neal Warshoff, Lewis Wesselius, Gordon Yung

ISABELA 2

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Canada: Deborah Assayag, Anil Dhar, Nasreen Khalil, Julie Morisset, Steeve Provencher, Chris Ryerson, Shane Shapera

France: Arnaud Bourdin, Bruno Crestani, Francois Lebargy, Martine Reynaud-Gaubert

Germany: Francesco Tommaso Bonella, Martin Claussen, Peter Hammerl, Christian Karagiannidis, Claus Keller, Winfried Randerath, Beate Stubbe

Hungary: Eszter Csánky, Balazs Medgyasszay, Veronika Muller

Israel: Yochai Adir, Amir Bar-Shai, Neville Berkman, Gershon Fink, Mordechai Kramer, David Shitrit

Italy: Elena Bargagli, Stefano Gasparini, Sergio Harari, Claudia Ravaglia, Luca Richeldi, Carlo Vancheri

Japan: Masahito Ebina, Masaki Fujita, Kazuya Ichikado, Yoshikazu Inoue, Nobuhisa Ishikawa, Shinyu Izumi, Motoyasu Kato, Tetsuji Kawamura, Yasuhiro Kondoh, Yasuhiko Nishioka, Takashi Ogura, Masaki Okamoto, Isoko Owan, Takefumi Saito, Noriho Sakamoto, Koji Sakamoto, Masahiro Shirai, Takafumi Suda, Keisuke Tomii

Republic of Korea: Man Pyo Chung, Sung Hwan Jeong, Choon Sik Park, Jong Sun Park, Jin Woo Song, Soo-Taek Uh

Mexico: Uriel Chavarria Martinez, Efrain Montano Gonzalez, Alicia Ramirez, Moises Eduardo Selman Lama

The Netherlands: Paul Bresser, Henk Kramer, Remy Mostard, Esther Nossent, Marcel Veltkamp, Marlies Wijsenbeek

New Zealand: Lutz Beckert, Catherina L Chang, Andrew Veale, Margaret Wilsher

Poland: Michal Bednarek, Grzegorz Gasior, Grazyna Jasieniak-Pinis, Ewa Jassem, Robert Mroz, Wojciech Piotrowski

South Africa: Ismail Abdullah, Anish Ambaram, Elvis Irusen, Michael Van der Linden, Richard van Zyl-Smit, Paul Williams

United States: James Allen, Francis Averill, Elizabeth Belloli, Anne Brown, Amy Case, Sachin Chaudhary, Gerard Criner, Kevin DeBoer, Daniel Dilling, Jeffrey Dorf, Richard Enelow, Neil Ettinger, Jeremy Feldman, Kevin Gibson, Jeffrey Golden, Mark Hamblin, Gary Hunninghake, Raj Karunakara, Hyun Kim, Tracy Luckhardt, Prema Menon, Lake Morrison, Justin Oldham, Nina Patel, Shelley Schmidt, Mary Strek, Ross Summer, Robert Sussman, James Tita, Srihari Veeraraghavan, Timothy Whelan, Joseph Zibrak

eTable 1. Baseline demographics and disease characteristics by strata

	ISABELA 1			ISABELA 2		
	Pirfenidone (n=208)	**Nintedanib (n=181)**	**Neither (n=134)**	**Pirfenidone (n=252)**	**Nintedanib (n=271)**	**Neither (n=254)**
Age, years	70.1 (6.8)	69.3 (7.2)	70.8 (7.7)	69.7 (6.9)	69.2 (7.0)	70.5 (7.2)
Male, n (%)	179 (86.1)	157 (86.7)	95 (70.9)	198 (78.6)	234 (86.3)	199 (78.3)
Race, n (%)						
American Indian or Alaska native	11 (5.3)	1 (0.6)	10 (7.5)	0[a]	0[b]	5 (2.0)[a]
Asian	4 (1.9)	16 (8.8)	9 (6.7)	67 (26.9)[a]	53 (20.6)[b]	92 (36.9)[a]
Black or African American	1 (0.5)	0	0	2 (0.8)[a]	1 (0.4)[b]	0[a]
Multiple	0	0	0	0[a]	0[b]	3 (1.2)[a]
Native Hawaiian or Other Pacific Islander	0	0	0	1 (0.4)[a]	1 (0.4)[b]	0[a]
White	192 (92.3)	164 (90.6)	115 (85.8)	179 (71.9)[a]	202 (78.6)[b]	149 (59.8)[a]
Former smoker, n (%)	125 (60.1)	122 (67.4)	75 (56.0)	184 (73.0)	207 (76.4)	164 (64.6)
BMI, kg/m^2	28.3 (3.9)	27.7 (3.9)	27.7 (3.8)	27.3 (3.9)	27.0 (4.2)	26.9 (3.8)
Duration of IPF, years	2.4 (1.5)	2.4 (1.4)	1.8 (1.3)[c]	2.6 (1.5)	2.4 (1.3)[d]	1.8 (1.5)
FVC, mL	2900.1 (788.4)	2990.3 (738.3)	2860.1 (863.1)	2678.7 (753.7)	2897.7 (794.9)[e]	2709.1 (744.8)
Percent predicted FVC, %	76.9 (16.1)	77.4 (16.1)	85.6 (18.7)	75.0 (15.5)	77.0 (17.1)[e]	79.9 (16.4)
FEV_1/FVC ratio, %	83.3 (4.9)	81.6 (5.4)	81.6 (6.0)	83.3 (5.9)	82.5 (5.6)[e]	82.6 (5.9)
SGRQ total score, %	34.1 (16.5)[f]	33.8 (17.6)	38.4 (21.9)	36.8 (19.1)[a]	34.3 (18.5)[g]	37.4 (21.9)

	ISABELA 1			ISABELA 2		
	Pirfenidone (n=208)	**Nintedanib (n=181)**	**Neither (n=134)**	**Pirfenidone (n=252)**	**Nintedanib (n=271)**	**Neither (n=254)**
6MWT distance, m	418.3 (108.0)	406.0 (110.1)	390.3 (107.1)[c]	403.8 (109.7)[a]	417.7 (99.0)[g]	382.0 (138.3)
Percent predicted DLCO corrected for hemoglobin, %	52.2 (15.4)	51.0 (15.9)	62.7 (19.1)	51.3 (17.4)[h]	52.5 (19.1)[g]	60.8 (21.2)[i]

[a] n=249; [b] n=257; [c] n=133; [d] n=270; [e] n=269; [f] n=206; [g] n=270; [h] n=251; [i] n=253.
Full analysis set. Values are mean (SD) unless otherwise stated.
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.

eTable 2. Duration of treatment and exposure (until the end of the studies)

	ISABELA 1				ISABELA 2			
	Ziritaxestat 600 mg (n=174)	**Ziritaxestat 200 mg (n=175)**	**Placebo (n=174)**	**Total (N=523)**	**Ziritaxestat 600 mg (n=259)**	**Ziritaxestat 200 mg (n=260)**	**Placebo (n=258)**	**Total (N=777)**
Overall compliance, mean[a]								
Mean (SD), %	94.3 (13.9)	96.5 (10.2)	97.9 (6.2)	96.2 (10.7)	93.7 (12.0)	96.5 (9.7)	97.6 (7.4)	95.9 (10.0)
Median (min, max), %	100.0 (15, 100)	100.0 (35, 101)	100.0 (63, 102)	100.0 (15, 102)	100.0 (42, 100)	100.0 (30, 100)	100.0 (46, 100)	100.0 (30, 100)
Total treatment duration, mean (SD), days	325.3 (197.7)	356.0 (185.6)	353.4 (180.2)	344.9 (188.1)	332.9 (165.7)	336.9 (159.2)	346.2 (156.8)	338.7 (160.5)
Exposure to study drug, patient-years	154.98	170.56	168.35	493.88	236.04	239.83	244.56	720.43
Exposure to pirfenidone, patient-years	69.04	77.15	72.86	219.05	93.25	95.76	94.25	283.26
Exposure to nintedanib, patient-years	57.03	58.47	64.28	179.78	87.40	88.56	100.40	276.36

[a] 100 x (number of tablets actually used) / (number of tablets that should have been used according to the randomization).
SD, standard deviation.

eTable 3. Doses of standard of care during the study period[a]

	ISABELA 1, n/N (%)				ISABELA 2, n/N (%)			
	Ziritaxestat 600 mg	**Ziritaxestat 200 mg**	**Placebo**	**Total**	**Ziritaxestat 600 mg**	**Ziritaxestat 200 mg**	**Placebo**	**Total**
Pirfenidone mean daily dose								
<1200 mg	10/72 (13.9)	12/78 (15.4)	6/73 (8.2)	28/223 (12.6)	20/95 (21.1)	12/95 (12.6)	6/86 (7.0)	38/276 (13.8)
1200–1800 mg	8/72 (11.1)	8/78 (10.3)	5/73 (6.8)	21/223 (9.4)	32/95 (33.7)	37/95 (38.9)	25/86 (29.1)	94/276 (34.1)
>1800 mg	54/72 (75.0)	58/78 (74.4)	62/73 (84.9)	174/223 (78.0)	43/95 (45.3)	46/95 (48.4)	55/86 (64.0)	144/276 (52.2)
Nintedanib mean daily dose								
≤200 mg	16/66 (24.2)	11/66 (16.7)	7/63 (11.1)	34/195 (17.4)	35/96(36.5)	20/96 (20.8)	14/98 (14.3)	69/290 (23.8)
200–300 mg	16/66 (24.2)	20/66 (30.3)	22/63 (34.9)	58/195 (29.7)	37/96 (38.5)	31/96 (32.3)	38/98 (38.8)	106/290 (36.6)
≥300 mg	34/66 (51.5)	35/66 (53.0)	34/63 (54.0)	103/195 (52.8)	24/96 (25.0)	45/96 (46.9)	46/98 (46.9)	115/290 (39.7)

[a] The intake of pirfenidone and nintedanib was measured on Day 1, at Week 26 and Week 52.
Full analysis set.
Denominator is the number of patients on pirfenidone or nintedanib in each treatment arm.

eTable 4. Number of patients who switched standard of care (until the end of the studies)

	ISABELA 1, n/N (%)				ISABELA 2, n/N (%)			
	Ziritaxestat 600 mg	**Ziritaxestat 200 mg**	**Placebo**	**Total**	**Ziritaxestat 600 mg**	**Ziritaxestat 200 mg**	**Placebo**	**Total**
Switch from pirfenidone to nintedanib	3/69 (4.3)	0	1/69 (1.4)	4/208 (1.9)	3/84 (3.6)	0	1/83 (1.2)	4/252 (1.6)
Switch from nintedanib to pirfenidone	3/60 (5.0)	4/61 (6.6)	2/60 (3.3)	9/181 (5.0)	9/89 (10.1)	7/91 (7.7)	0	16/271 (5.9)
Switch from neither to pirfenidone	0	4/44 (9.1)	2/45 (4.4)	6/134 (4.5)	2/86 (2.3)	3/84 (3.6)	3/84 (3.6)	8/254 (3.1)
Switch from neither to nintedanib	3/45 (6.7)	5/44 (11.4)	2/45 (4.4)	10/134 (7.5)	4/86 (4.7)	5/84 (6.0)	6/84 (7.1)	15/254 (5.9)

Full analysis set.

eTable 5. Primary cause of adjudicated all-cause hospitalization

	ISABELA 1			ISABELA 2		
Primary cause of hospitalization, n (%)	**Ziritaxestat 600 mg (n=169)**	**Ziritaxestat 200 mg (n=171)**	**Placebo (n=164)**	**Ziritaxestat 600 mg (n=259)**	**Ziritaxestat 200 mg (n=260)**	**Placebo (n=258)**
Respiratory related						
IPF exacerbation	2 (1.2)	6 (3.5)	6 (3.7)	14 (5.4)	5 (1.9)	5 (1.9)
Respiratory related – other	8 (4.7)	5 (2.9)	8 (4.9)	11 (4.2)	19 (7.3)	5 (1.9)
Respiratory related – extra parenchymal	0	2 (1.2)	1 (0.6)	1 (0.4)	1 (0.4)	1 (0.4)
Total	10 (5.9)	13 (7.6)	15 (9.1)	26 (10.0)	25 (9.6)	11 (4.3)
Non-respiratory related						
Cardiovascular	5 (3.0)	2 (1.2)	4 (2.4)	3 (1.2)	5 (1.9)	7 (2.7)
Cerebrovascular	0	3 (1.8)	1 (0.6)	2 (0.8)	3 (1.2)	1 (0.4)
Gastrointestinal[a]	1 (0.6)	5 (2.9)	2 (1.2)	4 (1.5)	3 (1.2)	3 (1.2)
Hemorrhage – not cardiovascular	0	0	0	2 (0.8)	0	0
Hepatobiliary[a]	1 (0.6)	2 (1.2)	1 (0.6)	0	1 (0.4)	1 (0.4)
Infection (includes sepsis)	1 (0.6)	1 (0.6)	0	0	2 (0.8)	1 (0.4)
Inflammatory/immune (includes autoimmune)	0	1 (0.6)	0	0	0	0
Malignancy (non-cardiovascular death attributable to leukemia, lymphoma or other malignancy	2 (1.2)	0	0	2 (0.8)	1 (0.4)	1 (0.4)
Neurological[a]	0	1 (0.6)	2 (1.2)	0	1 (0.4)	0
Non-cardiovascular procedure or surgery	1 (0.6)	1 (0.6)	0	1 (0.4)	1 (0.4)	1 (0.4)

	ISABELA 1			ISABELA 2		
Primary cause of hospitalization, n (%)	**Ziritaxestat 600 mg (n=169)**	**Ziritaxestat 200 mg (n=171)**	**Placebo (n=164)**	**Ziritaxestat 600 mg (n=259)**	**Ziritaxestat 200 mg (n=260)**	**Placebo (n=258)**
Non-prescription drug reaction or overdose	0	1 (0.6)	0	0	0	0
Other non-respiratory	2 (1.2)	1 (0.6)	1 (0.6)	4 (1.5)	2 (0.8)	0
Pancreatic[a]	0	1 (0.6)	0	0	0	1 (0.4)
Prescription drug reaction or overdose (includes anaphylaxis)	0	0	0	0	0	1 (0.4)
Renal	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.4)	2 (0.8)	2 (0.8)
Trauma	1 (0.6)	1 (0.6)	0	0	0	0
Total	15 (8.9)	21 (12.3)	12 (7.3)	19 (7.3)	21 (8.1)	19 (7.4)
Other						
Not a charter-defined event	0	2 (1.2)	1 (0.6)	0	2 (0.8)	2 (0.8)
Undetermined cause	3 (1.8)	1 (0.6)	2 (1.2)	4 (1.5)	0	2 (0.8)
Total	3 (1.8)	3 (1.8)	3 (1.8)	4 (1.5)	2 (0.8)	4 (1.6)

[a] Excludes malignancy.
IPF, idiopathic pulmonary fibrosis.

eTable 6. Change from baseline at Week 52 in efficacy endpoints

	ISABELA 1					ISABELA 2				
	Ziritaxest 600 mg (n=174)	**Ziritaxest 200 mg (n=175)**	**Placebo (n=174)**	**Difference between ziritaxestat 600 mg and placebo**	**Difference between ziritaxestat 200 mg and Placebo**	**Ziritaxest 600 mg (n=259)**	**Ziritaxest 200 mg (n=260)**	**Placebo (n=258)**	**Difference between ziritaxestat 600 mg and placebo**	**Difference between ziritaxestat 200 mg and placebo**
SGRQ total score, mean (95% CI), %	2.0 (–1.7, 5.7)	4.1 (1.6, 6.7)	3.0 (0.3, 5.8)	–1.0 (–5.6, 3.5)	1.1 (–2.6, 4.8)	4.8 (2.5, 7.0)	3.4 (1.1, 5.8)	3.8 (1.3, 6.2)	1.0 (–2.3, 4.3)	–0.3 (–3.7, 3.0)
6MWT distance, mean (95% CI), m	–36.3 (–51.9, –20.8)	–15.6 (–35.3, 4.0)	–34.7 (–57.7, –11.8)	–1.6 (–28.9, 25.7)	19.1 (–10.7, 48.9)	–14.5 (–27.6, –1.4)	–36.3 (–66.8, –5.8)	–22.6 (–34.7, –10.4)	8.1 (–9.6, 25.8)	–13.8 (–46.2, 18.7)

Full analysis set.
6MWT, 6-minute walk test; CI, confidence interval; SGRQ, St George's Respiratory Questionnaire.

eTable 7. Adjudicated all-cause mortality events in ISABELA 1 and 2

	ISABELA 1		
Primary cause of death, n (%)	**Ziritaxestat 600 mg (n=169)**	**Ziritaxestat 200 mg (n=171)**	**Placebo (n=164)**
Respiratory related			
IPF exacerbation	2 (1.2)	1 (0.6)	1 (0.6)
Respiratory related – other	4 (2.4)	5 (2.9)	2 (1.2)
Total	6 (3.6)	6 (3.5)	3 (1.8)
Non-respiratory related			
Cardiovascular	1 (0.6)	0	2 (1.2)
Malignancy[a]	2 (1.2)	0	0
Neurological[b]	0	0	1 (0.6)
Total	3 (1.8)	0	3 (1.8)
Other			
Undetermined cause	3 (1.8)	1 (0.6)	2 (1.2)
Total	3 (1.8)	1 (0.6)	2 (1.2)
	ISABELA 2		
Primary cause of death, n (%)	**Ziritaxestat 600 mg (n=259)**	**Ziritaxestat 200 mg (n=260)**	**Placebo (n=258)**
Respiratory related			
IPF exacerbation	4 (1.5)	2 (0.8)	1 (0.4)
Respiratory related – other	9 (3.5)	9 (3.5)	3 (1.2)
Meets charter definition of a respiratory related extra parenchymal death	2 (0.8)	0	0
Total	15 (5.8)	11 (4.2)	4 (1.6)
Non-respiratory related			
Cardiovascular	0	2 (0.8)	2 (0.8)
Cerebrovascular	1 (0.4)	0	0
Gastrointestinal[b]	0	1 (0.4)	0
Malignancy[a]	0	0	1 (0.4)
Total	1 (0.4)	3 (1.2)	3 (1.2)

Primary cause of death, n (%)	Ziritaxestat 600 mg (n=259)	Ziritaxestat 200 mg (n=260)	Placebo (n=258)
Other			
Undetermined cause	5 (1.9)	4 (1.5)	3 (1.2)
Total	5 (1.9)	4 (1.5)	3 (1.2)

[a] Non-cardiovascular death attributable to leukemia, lymphoma or other malignancy. [b] Excludes malignancy.
Full analysis set. Adjudicated events that occurred during the trials (deaths collected via vital status forms were not included).
IPF, idiopathic pulmonary fibrosis.

eTable 8. Treatment-emergent adverse events and dose reductions/interruptions/discontinuations according to stratum in ISABELA 1 and 2

	ISABELA 1								
	Pirfenidone			Nintedanib			Neither		
Patients, n (%)	**Ziritaxestat 600 mg (n=69)**	**Ziritaxestat 200 mg (n=70)**	**Placebo (n=69)**	**Ziritaxestat 600 mg (n=60)**	**Ziritaxestat 200 mg (n=61)**	**Placebo (n=60)**	**Ziritaxestat 600 mg (n=45)**	**Ziritaxestat 200 mg (n=44)**	**Placebo (n=45)**
TEAE	48 (69.6)	60 (85.7)	62 (89.9)	57 (95.0)	52 (85.2)	50 (83.3)	32 (71.1)	36 (81.8)	35 (77.8)
Serious TEAE	17 (24.6)	13 (18.6)	15 (21.7)	14 (23.3)	16 (26.2)	13 (21.7)	7 (15.6)	9 (20.5)	8 (17.8)
Death	3 (4.3)	3 (4.3)	4 (5.8)	3 (5.0)	2 (3.3)	1 (1.7)	2 (4.4)	1 (2.3)	3 (6.7)
Worst TEAE severity									
Mild	7 (10.1)	12 (17.1)	13 (18.8)	5 (8.3)	9 (14.8)	7 (11.7)	2 (4.4)	12 (27.3)	9 (20.0)
Moderate	24 (34.8)	30 (42.9)	33 (47.8)	35 (58.3)	26 (42.6)	29 (48.3)	23 (51.1)	13 (29.5)	18 (40.0)
Severe	12 (17.4)	14 (20.0)	12 (17.4)	14 (23.3)	11 (18.0)	9 (15.0)	3 (6.7)	10 (22.7)	5 (11.1)
Life-threatening	1 (1.4)	1 (1.4)	0	0	4 (6.6)	4 (6.7)	2 (4.4)	0	0
Death	4 (5.8)	3 (4.3)	4 (5.8)	3 (5.0)	2 (3.3)	1 (1.7)	2 (4.4)	1 (2.3)	3 (6.7)
Treatment-related TEAE to study drug	16 (23.2)	17 (24.3)	24 (34.8)	35 (58.3)	25 (41.0)	19 (31.7)	9 (20.0)	11 (25.0)	10 (22.2)
Treatment-related TEAE to pirfenidone	15 (21.7)	21 (30.0)	18 (26.1)	5 (8.3)	5 (8.2)	6 (10.0)	2 (4.4)	2 (4.5)	2 (4.4)
Treatment-related TEAE to nintedanib	4 (5.8)	7 (10.0)	6 (8.7)	42 (70.0)	27 (44.3)	18 (30.0)	4 (8.9)	5 (11.4)	2 (4.4)

	Pirfenidone			Nintedanib			Neither		
Patients, n (%)	**Ziritaxestat 600 mg (n=69)**	**Ziritaxestat 200 mg (n=70)**	**Placebo (n=69)**	**Ziritaxestat 600 mg (n=60)**	**Ziritaxestat 200 mg (n=61)**	**Placebo (n=60)**	**Ziritaxestat 600 mg (n=45)**	**Ziritaxestat 200 mg (n=44)**	**Placebo (n=45)**
Study drug									
Reduced	0	1 (1.4)	0	7 (11.7)	4 (6.6)	2 (3.3)	2 (4.4)	1 (2.3)	1 (2.2)
Interrupted	6 (8.7)	8 (11.4)	4 (5.8)	17 (28.3)	15 (24.6)	10 (16.7)	7 (15.6)	6 (13.6)	9 (20.0)
Permanently stopped	7 (10.1)	2 (2.9)	8 (11.6)	8 (13.3)	6 (9.8)	4 (6.7)	3 (6.7)	2 (4.5)	1 (2.2)
Pirfenidone									
Reduced	1 (1.4)	2 (2.9)	2 (2.9)	0	0	0	0	1 (2.3)	1 (2.2)
Interrupted	2 (2.9)	3 (4.3)	5 (7.2)	1 (1.7)	0	0	1 (2.2)	1 (2.3)	0
Permanently stopped	3 (4.3)	2 (2.9)	4 (5.8)	0	0	0	0	0	0
Nintedanib									
Reduced	1 (1.4)	0	0	6 (10.0)	3 (4.9)	6 (10.0)	0	0	0
Interrupted	1 (1.4)	0	0	12 (20.0)	8 (13.1)	10 (16.7)	0	2 (4.5)	0
Permanently stopped	1 (1.4)	0	0	2 (3.3)	4 (6.6)	0	1 (2.2)	2 (4.5)	0

	ISABELA 2								
	Pirfenidone			Nintedanib			Neither		
Patients, n (%)	**Ziritaxestat 600 mg (n=84)**	**Ziritaxestat 200 mg (n=85)**	**Placebo (n=83)**	**Ziritaxestat 600 mg (n=89)**	**Ziritaxestat 200 mg (n=91)**	**Placebo (n=91)**	**Ziritaxestat 600 mg (n=86)**	**Ziritaxestat 200 mg (n=84)**	**Placebo (n=84)**
TEAE	65 (77.4)	72 (84.7)	67 (80.7)	85 (95.5)	80 (87.9)	73 (80.2)	60 (69.8)	71 (84.5)	55 (65.5)
Serious TEAE	25 (29.8)	25 (29.4)	14 (16.9)	23 (25.8)	19 (20.9)	15 (16.5)	16 (18.6)	19 (22.6)	13 (15.5)
Death	8 (9.5)	9 (10.6)	4 (4.8)	5 (5.6)	5 (5.5)	1 (1.1)	9 (10.5)	6 (7.1)	5 (6.0)
Worst TEAE severity									
Mild	11 (13.1)	11 (12.9)	10 (12.0)	13 (14.6)	22 (24.2)	18 (19.8)	10 (11.6)	17 (20.2)	12 (14.3)
Moderate	30 (35.7)	37 (43.5)	40 (48.2)	46 (51.7)	38 (41.8)	39 (42.9)	35 (40.7)	33 (39.3)	29 (34.5)
Severe	15 (17.9)	14 (16.5)	12 (14.5)	18 (20.2)	15 (16.5)	14 (15.4)	5 (5.8)	15 (17.9)	7 (8.3)
Life-threatening	1 (1.2)	1 (1.2)	1 (1.2)	3 (3.4)	0	1 (1.1)	1 (1.2)	0	2 (2.4)
Death	8 (9.5)	9 (10.6)	4 (4.8)	5 (5.6)	5 (5.5)	1 (1.1)	9 (10.5)	6 (7.1)	5 (6.0)
Treatment-related TEAE to study drug	21 (25.0)	16 (18.8)	23 (27.7)	63 (70.8)	47 (51.6)	32 (35.2)	12 (14.0)	17 (20.2)	15 (17.9)
Treatment-related TEAE to pirfenidone	12 (14.3)	23 (27.1)	23 (27.7)	3 (3.4)	6 (6.6)	4 (4.4)	4 (4.7)	5 (6.0)	3 (3.6)
Treatment-related TEAE to nintedanib	5 (6.0)	4 (4.7)	3 (3.6)	70 (78.7)	44 (48.4)	36 (39.6)	5 (5.8)	6 (7.1)	3 (3.6)

	Pirfenidone			Nintedanib			Neither		
Patients, n (%)	**Ziritaxestat 600 mg (n=84)**	**Ziritaxestat 200 mg (n=85)**	**Placebo (n=83)**	**Ziritaxestat 600 mg (n=89)**	**Ziritaxestat 200 mg (n=91)**	**Placebo (n=91)**	**Ziritaxestat 600 mg (n=86)**	**Ziritaxestat 200 mg (n=84)**	**Placebo (n=84)**
Study drug									
Reduced	3 (3.6)	0	2 (2.4)	24 (27.0)	9 (9.9)	7 (7.7)	3 (3.5)	3 (3.6)	0
Interrupted	15 (17.9)	11 (12.9)	7 (8.4)	33 (37.1)	14 (15.4)	14 (15.4)	9 (10.5)	12 (14.3)	12 (14.3)
Permanently stopped	9 (10.7)	7 (8.2)	7 (8.4)	15 (16.9)	12 (13.2)	5 (5.5)	5 (5.8)	8 (9.5)	6 (7.1)
Pirfenidone									
Reduced	4 (4.8)	5 (5.9)	2 (2.4)	1 (1.1)	1 (1.1)	0	0	0	0
Interrupted	6 (7.1)	8 (9.4)	5 (6.0)	2 (2.2)	0	0	0	1 (1.2)	0
Permanently stopped	7 (8.3)	2 (2.4)	7 (8.4)	1 (1.1)	1 (1.1)	0	0	0	1 (1.2)
Nintedanib									
Reduced	1 (1.2)	0	0	23 (25.8)	6 (6.6)	10 (11.0)	0	2 (2.4)	0
Interrupted	1 (1.2)	0	0	24 (27.0)	17 (18.7)	13 (14.3)	0	2 (2.4)	1 (1.2)
Permanently stopped	0	0	0	10 (11.2)	3 (3.3)	1 (1.1)	0	0	1 (1.2)

Full analysis set.
Events listed in the table occurred during the trial, on or after the start of study drug intake and no later than 30 days after the last dose of study drug.
TEAE, treatment-emergent adverse event.

eTable 9. Treatment-emergent adverse events with a ≥5% incidence in at least one treatment group in ISABELA 1 and 2

	ISABELA 1		
Patients, n (%)	**Ziritaxestat 600 mg (n=174)**	**Ziritaxestat 200 mg (n=175)**	**Placebo (n=174)**
TEAE	137 (78.7)	148 (84.6)	147 (84.5)
Gastrointestinal disorders			
Diarrhea	51 (29.3)	41 (23.4)	20 (11.5)
Gastroesophageal reflux disease	9 (5.2)	3 (1.7)	2 (1.1)
Nausea	16 (9.2)	14 (8.0)	10 (5.7)
General disorders and administration-site conditions			
Fatigue	10 (5.7)	9 (5.1)	6 (3.4)
Infections and infestations			
Bronchitis	8 (4.6)	11 (6.3)	4 (2.3)
Nasopharyngitis	11 (6.3)	7 (4.0)	10 (5.7)
Upper respiratory tract infection	10 (5.7)	12 (6.9)	11 (6.3)
Musculoskeletal and connective tissue disorders			
Back pain	3 (1.7)	9 (5.1)	9 (5.2)
Nervous system disorders			
Dizziness	8 (4.6)	5 (2.9)	9 (5.2)
Headache	9 (5.2)	13 (7.4)	10 (5.7)
Respiratory, thoracic and mediastinal disorders			
Cough	16 (9.2)	21 (12.0)	16 (9.2)
Dyspnea	10 (5.7)	17 (9.7)	10 (5.7)
IPF	21 (12.1)	15 (8.6)	21 (12.1)
	ISABELA 2		
Patients, n (%)	**Ziritaxestat 600 mg (n=259)**	**Ziritaxestat 200 mg (n=260)**	**Placebo (n=258)**
TEAE	210 (81.1)	223 (85.8)	195 (75.6)
Gastrointestinal disorders			
Diarrhea	74 (28.6)	58 (22.3)	47 (18.2)
Nausea	23 (8.9)	16 (6.2)	13 (5.0)

Patients, n (%)	Ziritaxestat 600 mg (n=259)	Ziritaxestat 200 mg (n=260)	Placebo (n=258)
Infections and infestations			
Bronchitis	14 (5.4)	11 (4.2)	4 (1.6)
Nasopharyngitis	16 (6.2)	16 (6.2)	13 (5.0)
Upper respiratory tract infection	19 (7.3)	22 (8.5)	17 (6.6)
Investigations			
Weight decreased	14 (5.4)	9 (3.5)	8 (3.1)
Metabolism and nutrition disorders			
Decreased appetite	20 (7.7)	14 (5.4)	9 (3.5)
Musculoskeletal and connective tissue disorders			
Back pain	13 (5.0)	6 (2.3)	6 (2.3)
Nervous system disorders			
Headache	16 (6.2)	14 (5.4)	15 (5.8)
Respiratory, thoracic and mediastinal disorders			
Cough	24 (9.3)	21 (8.1)	22 (8.5)
Dyspnea	14 (5.4)	13 (5.0)	22 (8.5)
IPF	36 (13.9)	31 (11.9)	21 (8.1)

Full analysis set.
IPF, idiopathic pulmonary fibrosis; TEAE, treatment-emergent adverse event.

eTable 10. Treatment-emergent adverse events leading to death in ISABELA 1 and 2

	ISABELA 1		
System organ class and preferred term, n (%)	**Ziritaxestat 600 mg (n=174)**	**Ziritaxestat 200 mg (n=175)**	**Placebo (n=174)**
TEAE leading to death	8 (4.6)	6 (3.4)	8 (4.6)
Cardiac disorders			
Acute myocardial infarction	0	0	1 (0.6)
Cardiac failure congestive	0	1 (0.6)	0
Myocardial infarction	1 (0.6)	0	0
Myocardial rupture	0	0	1 (0.6)
Pericardial hemorrhage	0	0	1 (0.6)
Total	1 (0.6)	1 (0.6)	1 (0.6)
General disorders and administration-site conditions			
Sudden death	0	1 (0.6)	0
Total	0	1 (0.6)	0
Infections and infestations			
COVID-19 pneumonia	0	2 (1.1)	0
Lower respiratory tract infections	0	0	1 (0.6)
Pneumonia	2 (1.1)	0	0
Suspected COVID-19	0	0	1 (0.6)
Total	2 (1.1)	2 (1.1)	2 (1.1)
Nervous system disorders			
Limbic encephalitis	0	0	1 (0.6)
Total	0	0	1 (0.6)
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure	0	1 (0.6)	1 (0.6)
IPF	4 (2.3)	1 (0.6)	3 (1.7)
Pulmonary embolism	1 (0.6)	0	0
Total	5 (2.9)	2 (1.1)	4 (2.3)

	ISABELA 2		
System organ class and preferred term, n (%)	**Ziritaxestat 600 mg (n=259)**	**Ziritaxestat 200 mg (n=260)**	**Placebo (n=258)**
No TEAE leading to death	237 (91.5)	240 (92.3)	248 (96.1)
TEAE leading to death	22 (8.5)	20 (7.7)	10 (3.9)
Cardiac disorders			
Acute cardiac event	0	1 (0.4)	0
Acute myocardial infarction	1 (0.4)	1 (0.4)	0
Cardiac arrest	0	1 (0.4)	0
Cardiac failure acute	0	0	1 (0.4)
Cardiogenic shock	0	0	1 (0.4)
Myocardial infarction	0	1 (0.4)	2 (0.8)
Total	1 (0.4)	4 (1.5)	4 (1.6)
Gastrointestinal disorders			
Intestinal ischemia	0	1 (0.4)	0
Total	0	1 (0.4)	0
General disorders and administration-site conditions			
Death	1 (0.4)	1 (0.4)	1 (0.4)
Total	1 (0.4)	1 (0.4)	1 (0.4)
Infections and infestations			
COVID-19	2 (0.8)	4 (1.5)	0
COVID-19 pneumonia	1 (0.4)	1 (0.4)	0
Pneumonia	4 (1.5)	1 (0.4)	2 (0.8)
Pneumonia, bacterial	1 (0.4)	0	0
Total	8 (3.1)	6 (2.3)	2 (0.8)
Neoplasms, benign, malignant and unspecified[a]			
Lung adenocarcinoma stage IV	0	0	1 (0.4)
Total	0	0	1 (0.4)
Nervous system disorders			
Ischemic stroke	1 (0.4)	0	0
Total	1 (0.4)	0	0

System organ class and preferred term, n (%)	Ziritaxestat 600 mg (n=259)	Ziritaxestat 200 mg (n=260)	Placebo (n=258)
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome	0	2 (0.8)	0
Acute respiratory failure	0	2 (0.8)	1 (0.4)
Dyspnea	0	1 (0.4)	0
Hypoxia	0	1 (0.4)	0
IPF	5 (1.9)	3 (1.2)	1 (0.4)
Pneumothorax spontaneous	1 (0.4)	0	0
Respiratory distress	1 (0.4)	0	0
Respiratory failure	4 (1.5)	0	0
Total	11 (4.2)	9 (3.5)	2 (0.8)

[a] Includes cysts and polyps.
Full analysis set.
Deaths include adverse events reported as leading to death that occurred during the trial, on or after the start of study drug intake and no later than 30 days after the last dose of study drug.
IPF, idiopathic pulmonary fibrosis; TEAE, treatment-emergent adverse event.

eTable 11. Summary of adverse events leading to deaths

ISABELA 1		
Treatment group	**Stratum**	**Cause of death (as provided verbatim by investigator)**
Ziritaxestat 600 mg	Nintedanib	Colon tumor
Ziritaxestat 600 mg	Nintedanib	Bilateral pneumonia
Ziritaxestat 600 mg	Neither	Worsening of IPF
Ziritaxestat 600 mg	Nintedanib	Pneumonia
Ziritaxestat 600 mg	Pirfenidone	Progression of IPF
Ziritaxestat 600 mg	Nintedanib	Lung squamous-cell carcinoma, metastatic
Ziritaxestat 600 mg	Pirfenidone	Hypoxemic respiratory failure
Ziritaxestat 600 mg	Pirfenidone	Unknown cause of death – cardiac arrest
Ziritaxestat 600 mg	Pirfenidone	Pulmonary embolism
Ziritaxestat 600 mg	Neither	IPF with acute exacerbation
Ziritaxestat 600 mg	Nintedanib	IPF progression
Ziritaxestat 600 mg	Pirfenidone	Myocardial infarction
Ziritaxestat 200 mg	Pirfenidone	Decompensated congestive heart failure
Ziritaxestat 200 mg	Neither	Pneumonia by COVID-19
Ziritaxestat 200 mg	Nintedanib	COVID-19 pneumonia
Ziritaxestat 200 mg	Nintedanib	Major progression of lung fibrosis
Ziritaxestat 200 mg	Pirfenidone	Unknown cause of death
Ziritaxestat 200 mg	Pirfenidone	COVID-19 pneumonia
Ziritaxestat 200 mg	Pirfenidone	Worsening of IPF condition
Ziritaxestat 200 mg	Nintedanib	Acute respiratory failure with hypoxia
Placebo	Pirfenidone	Acute exacerbation of IPF
Placebo	Neither	Lower respiratory tract lung infection
Placebo	Neither	Progressive pulmonary fibrosis
Placebo	Neither	Suspected COVID-19 infection
Placebo	Pirfenidone	Acute respiratory failure
Placebo	Pirfenidone	Limbic encephalitis
Placebo	Pirfenidone	Acute IPF exacerbation
Placebo	Nintedanib	Acute myocardial infarction
Placebo	Nintedanib	Myocardial rupture/pericardial hemorrhage

ISABELA 2		
Treatment group	**Stratum**	**Cause of death**
Ziritaxestat 600 mg	Neither	Pneumonia
Ziritaxestat 600 mg	Neither	Bilateral spontaneous pneumothorax with pneumomediastinum and subcutaneous emphysema
Ziritaxestat 600 mg	Pirfenidone	IPF exacerbation
Ziritaxestat 600 mg	Pirfenidone	Acute exacerbation of IPF
Ziritaxestat 600 mg	Nintedanib	Acute exacerbation of IPF with acute respiratory hypoxic insufficiency
Ziritaxestat 600 mg	Nintedanib	COVID-19 infection coronavirus
Ziritaxestat 600 mg	Pirfenidone	Respiratory failure
Ziritaxestat 600 mg	Pirfenidone	COVID-19 pneumonia
Ziritaxestat 600 mg	Neither	Pneumonia
Ziritaxestat 600 mg	Pirfenidone	Pneumonia, bacterial
Ziritaxestat 600 mg	Neither	Acute myocardial infarction
Ziritaxestat 600 mg	Pirfenidone	Pneumonia
Ziritaxestat 600 mg	Neither	Acute respiratory distress
Ziritaxestat 600 mg	Neither	Respiratory failure
Ziritaxestat 600 mg	Neither	Respiratory failure
Ziritaxestat 600 mg	Neither	Hospitalization for IPF exacerbation
Ziritaxestat 600 mg	Pirfenidone	COVID-19 infection
Ziritaxestat 600 mg	Nintedanib	Worsening IPF
Ziritaxestat 600 mg	Pirfenidone	Exacerbation of IPF
Ziritaxestat 600 mg	Nintedanib	Right upper lobe pneumonia
Ziritaxestat 600 mg	Neither	Ischemic stroke
Ziritaxestat 600 mg	Nintedanib	Unknown cause of death (probable IPF)
Ziritaxestat 600 mg	Nintedanib	Acute hypoxic respiratory failure due to worsening if IPF
Ziritaxestat 200 mg	Neither	COVID-19 infection
Ziritaxestat 200 mg	Pirfenidone	Exacerbation of IPF
Ziritaxestat 200 mg	Neither	COVID-19 pneumonia
Ziritaxestat 200 mg	Nintedanib	Sudden death, most likely cardiac event
Ziritaxestat 200 mg	Nintedanib	Unknown cause of death
Ziritaxestat 200 mg	Pirfenidone	IPF acute exacerbation
Ziritaxestat 200 mg	Pirfenidone	Acute mesenteric ischemia

Treatment group	Stratum	Cause of death
Ziritaxestat 200 mg	Pirfenidone	Exacerbation of IPF
Ziritaxestat 200 mg	Neither	Adult respiratory difficulty syndrome, suspected coronavirus
Ziritaxestat 200 mg	Neither	Acute respiratory insufficiency
Ziritaxestat 200 mg	Pirfenidone	Heart attack
Ziritaxestat 200 mg	Pirfenidone	Unwitnessed cardiac arrest
Ziritaxestat 200 mg	Nintedanib	Hospitalization for worsening of IPF (followed by death)
Ziritaxestat 200 mg	Nintedanib	Pneumonia
Ziritaxestat 200 mg	Pirfenidone	COVID-19 infection cause of death (nose swab test was performed and test was positive)
Ziritaxestat 200 mg	Nintedanib	Increased dyspnea due to worsening IPF
Ziritaxestat 200 mg	Pirfenidone	COVID-19 infection
Ziritaxestat 200 mg	Pirfenidone	Hypoxemia
Ziritaxestat 200 mg	Pirfenidone	Worsening IPF
Ziritaxestat 200 mg	Nintedanib	Acute myocardial infarction/acute respiratory failure
Ziritaxestat 200 mg	Neither	Acute respiratory distress syndrome secondary to sepsis
Ziritaxestat 200 mg	Neither	COVID-19
Placebo	Pirfenidone	Pneumonia
Placebo	Neither	Cardiogenic shock
Placebo	Neither	Exacerbation of IPF
Placebo	Pirfenidone	Heart attack
Placebo	Pirfenidone	Acute heart failure
Placebo	Nintedanib	Myocardial infarction
Placebo	Neither	Suspected primary bronchial carcinoma
Placebo	Nintedanib	Metastatic adenocarcinoma of lung
Placebo	Neither	Pneumonia; lobes involved unknown
Placebo	Pirfenidone	NSCLC stage IV adenocarcinoma
Placebo	Neither	Acute chronic respiratory failure with hypoxia
Placebo	Neither	Unknown cause of death

COVID-19, coronavirus disease 2019; IPF, idiopathic pulmonary fibrosis; NSCLC, non-small cell lung cancer.

eTable 12. Treatment-emergent adverse events related to COVID-19 infections and suspected infections in ISABELA 1 and 2

	ISABELA 1		
System organ class and preferred term, n (%)	**Ziritaxestat 600 mg (n=174)**	**Ziritaxestat 200 mg (n=175)**	**Placebo (n=174)**
TEAE related to COVID-19 infection or suspected infection	4 (2.3)	7 (4.0)	7 (4.0)
Infections			
COVID-19 infection	2 (1.1)	3 (1.7)	5 (2.9)
COVID-19 pneumonia	1 (0.6)	3 (1.7)	0
Suspected COVID-19	0	0	1 (0.6)
Injury, poisoning or procedural complication			
Vaccination complication	0	1 (0.6)	0
Investigations			
SARS-CoV-2 test positive	0	1 (0.6)	0
Metabolism and nutrition disorders			
Hypertriglyceridemia	0	0	1 (0.6)
Respiratory, thoracic and mediastinal disorders			
Dyspnea	0	1 (0.6)	0
Respiratory failure	1 (0.6)	0	0
Skin and subcutaneous tissue disorders			
Drug eruption	1 (0.6)	0	0
	ISABELA 2		
System organ class and preferred term, n (%)	**Ziritaxestat 600 mg (n=259)**	**Ziritaxestat 200 mg (n=260)**	**Placebo (n=258)**
TEAE related to COVID-19 infection or suspected infection	14 (5.4)	11 (4.2)	6 (2.3)
Blood and lymphatic system disorders			
Anemia	0	0	1 (0.4)

System organ class and preferred term, n (%)	Ziritaxestat 600 mg (n=259)	Ziritaxestat 200 mg (n=260)	Placebo (n=258)
Infections			
Asymptomatic COVID-19	1 (0.4)	1 (0.4)	0
COVID-19	10 (3.9)	7 (2.7)	3 (1.2)
COVID-19 pneumonia	1 (0.4)	2 (0.8)	1 (0.4)
Influenzal pneumonia	1 (0.4)	0	0
Rhinitis	1 (0.4)	0	0
Investigations			
Amylase increased	0	0	1 (0.4)
Lipase increased	0	0	1 (0.4)
SARS-CoV-2 test positive	0	1 (0.4)	0
Nervous system disorders			
Dizziness	1 (0.4)	0	0
Renal and urinary disorders			
Renal impairment	1 (0.4)	0	0
Respiratory, thoracic and mediastinal disorders			9
Organizing pneumonia	1 (0.4)	0	0
Productive cough	1 (0.4)	0	0

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome-associated coronavirus 2; TEAE, treatment-emergent adverse event.

eTable 13. Impact of COVID-19 on study visits

	ISABELA 1			
Patients, n (%)	**Ziritaxestat 600 mg (n=174)**	**Ziritaxestat 200 mg (n=175)**	**Placebo (n=174)**	**Total (N=523)**
Number of missing or virtual visits due to COVID-19				
0	60 (34.5)	50 (28.6)	59 (33.9)	169 (32.3)
1	55 (31.6)	55 (31.4)	62 (35.6)	172 (32.9)
2	21 (12.1)	28 (16.0)	20 (11.5)	69 (13.2)
3	14 (8.0)	15 (8.6)	14 (8.0)	43 (8.2)
4	11 (6.3)	11 (6.3)	10 (5.7)	32 (6.1)
5	6 (3.4)	7 (4.0)	5 (2.9)	18 (3.4)
6	2 (1.1)	6 (3.4)	2 (1.1)	10 (1.9)
7	3 (1.7)	2 (1.1)	1 (0.6)	6 (1.1)
8	1 (0.6)	1 (0.6)	0	2 (0.4)
10	1 (0.6)	0	1 (0.6)	2 (0.4)
	ISABELA 2			
Patients, n (%)	**Ziritaxestat 600 mg (n=259)**	**Ziritaxestat 200 mg (n=260)**	**Placebo (n=258)**	**Total (N=777)**
Number of missing or virtual visits due to COVID-19				
0	93 (35.9)	108 (41.5)	93 (36.0)	294 (37.8)
1	78 (30.1)	75 (28.8)	78 (30.2)	231 (29.7)
2	36 (13.9)	33 (12.7)	31 (12.0)	100 (12.9)
3	18 (6.9)	20 (7.7)	21 (8.1)	59 (7.6)
4	14 (5.4)	10 (3.8)	15 (5.8)	39 (5.0)
5	9 (3.5)	7 (2.7)	13 (5.0)	29 (3.7)
6	5 (1.9)	3 (1.2)	3 (1.2)	11 (1.4)
7	3 (1.2)	0	2 (0.8)	5 (0.6)
8	1 (0.4)	3 (1.2)	1 (0.4)	5 (0.6)
9	2 (0.8)	1 (0.4)	1 (0.4)	4 (0.5)

COVID-19, coronavirus disease 2019.

eTable 14. Model-derived ziritaxestat pharmacokinetic parameters in ISABELA 1 and 2

SoC	Ziritaxestat dose, mg	AUC_{50th}, ng.mL/h	AUC_{5th}, ng.mL/h	AUC_{95th}, ng.mL/h	$C_{min50th}$, ng/mL	C_{min5th}, ng/mL	$C_{min95th}$, ng/mL	$C_{max50th}$, ng/mL	C_{max5th}, ng/mL	$C_{max95th}$, ng/mL
	ISABELA 1									
Neither	200	9622 (7327.66, 11916.34)	4895	27139	91 (59.84, 122.16)	40.96	428.9	807 (669.34, 944.66)	471	1712
	600	50832 (39988.6, 61675.4)	21592	109027	526 (368.71, 683.29)	183	1751	3966 (3336.35, 4595.65)	2040	6847
Nintedanib	200	9450 (8579.75, 10320.25)	5233	18567	98 (85.2, 110.8)	46.29	278.1	738 (688.56, 787.44)	469.2	1197
	600	42446 (36367.83, 48524.17)	19266	90414	461 (355.75, 566.25)	167.9	1557	3206 (2884.03, 3527.97)	1756	5503
Pirfenidone	200	5745 (5321.92, 6168.08)	2837	11910	49 (44.86, 53.14)	22.59	120.1	538 (505.84, 570.16)	296	947.6
	600	19820 (15485.36, 24154.64)	11779	60299	166 (122.55, 209.45)	94.08	670.6	1902 (1577.86, 2226.14)	1221	4494

SoC	Ziritaxestat dose, mg	AUC_{50th}, ng.mL/h	AUC_{5th}, ng.mL/h	AUC_{95th}, ng.mL/h	$C_{min50th}$, ng/mL	C_{min5th}, ng/mL	$C_{min95th}$, ng/mL	$C_{max50th}$, ng/mL	C_{max5th}, ng/mL	$C_{max95th}$, ng/mL
	ISABELA 2									
Neither	200	11558 (10475.95, 12640.05)	5905	20615	115 (99.9, 130.1)	50.6	270.3	927 (863.72, 990.28)	549.9	1409
	600	40776 (37010.42, 44541.58)	23842	95256	392 (343.94, 440.06)	204.9	1379	3368 (3136.15, 3599.85)	2211	6227
Nintedanib	200	10329 (9221.48, 11436.52)	4584	19053	111 (93.63, 128.37)	39.58	289.6	788 (726.61, 849.39)	422.7	1220
	600	44737 (40771.8, 48702.2)	17367	77193	498 (433.83, 562.17)	148.9	1191	3330 (3114.01, 3545.99)	1616	4913
Pirfenidone	200	5706 (5260.09, 6151.91)	3334	13245	49 (44.59, 53.41)	26.86	138.7	535 (501.49, 568.51)	340.5	1025
	600	22412 (20283.49, 24540.51)	12543	59954	191 (170.05, 211.95)	100.6	664.5	2104 (1943.01, 2264.99)	1289	4475

Pharmacokinetic analysis set.
Each parameter is presented as median, 5th and 95th percentiles of its stimulated distribution. Figures in parentheses are the 90th percentile CI of the median of the parameter.
AUC, area under the concentration–time curve; CI, confidence interval; C_{max}, maximum observed concentration at steady state; C_{min}, minimum (trough) observed plasma concentration; SoC, standard of care.

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