Supplementary methods.

Combination treatment administration

Over the 24-week combination treatment period, pirfenidone was continued at 1602–2403 mg/day (up to three 267-mg capsules three times daily), taken with food at the same times each day; and nintedanib was administered at 200–300 mg/day, taken with food at the same times each day. Nintedanib was titrated over the first 2 weeks from 100 mg/day during Week 1 (one 100-mg capsule once daily), to 200 mg/day during Week 2 (one 100-mg capsule twice daily [BID]) to a maintenance dose of 300 mg/day from Week 3 onwards (one 150-mg capsule BID). Twice-daily doses were taken approximately 12 hours apart.

For patients with a treatment interruption of <28 consecutive days, study treatment could be restarted at the discretion of the investigator. Patients who had study treatment interrupted for ≥28 consecutive days could not restart treatment in the study and were withdrawn.

Assessments

Physical examination findings, clinical laboratory tests, electrocardiograms, early treatment discontinuation (including reasons) and deaths and cause of deaths were also recorded. A patient diary was used to report TEAEs and investigators sought information on TEAEs at each patient visit. The patient diary was also used to record daily dosing adherence for both pirfenidone and nintedanib, and concomitant medication use from screening to final follow-up. Concomitant medications were coded according to the proprietary Genentech Drug Thesaurus (e.g. bronchodilators and antiasthmatics). Physical examinations were performed at screening, baseline (Day 1 of nintedanib treatment), Weeks 2, 4, 8, 12, 16, 20 and 24 and follow-up (or early discontinuation, if applicable). Clinical laboratory tests were undertaken at screening,

baseline, Weeks 1, 2, 3, 4, 8, 12, 16, 20 and 24 and follow-up (or early discontinuation, if applicable). TEAEs were coded to a preferred term and system organ class using the Medical Dictionary for Regulatory Activities (Version 20.0) and graded using the Common Terminology Criteria for Adverse Events, version 4.03 [1]. Investigators assessed whether each TEAE was related to pirfenidone, nintedanib, both or neither using their knowledge of the patient, the circumstances surrounding the event and an evaluation of any potential alternative causes. This assessment of TEAE causality considered the course of the event, known association of the event with the study drug or similar treatments, and with IPF, presence of risk factors or use of concomitant medications known to increase the occurrence of the event, and presence of non–treatment-related factors known to be associated with the event.

During combination treatment, nintedanib dosage was reduced or interrupted in patients who experienced new diarrhoea, vomiting or nausea TEAEs that persisted despite appropriate supportive care and symptomatic treatment (e.g. adequate hydration, antidiarrhoeal medication, antiemetic medication); whether pirfenidone dosage was maintained, reduced or interrupted was left to the judgement of the investigator. If diarrhoea, vomiting or nausea persisted for ≥28 days or was judged to be intolerable, nintedanib was discontinued and the patient was withdrawn from the study.

FVC and DLco were measured at screening, baseline and Weeks 12 and 24 (or early discontinuation, if applicable). An exploratory assessment of efficacy measured change in percent predicted FVC and DLco (as reported by the investigator) between baseline and Week 24. Historical values of percent predicted FVC and DLco closest to 6 months before start of screening were used as a comparison. Change in K-BILD score from baseline to Week 24 (or early discontinuation, if applicable) was also analysed in an exploratory analysis.

An independent data monitoring committee (iDMC) reviewed safety data and advised on study conduct three times during the study.

Sample size prediction

A sample size of approximately 80 patients was selected based on AE discontinuation rates after one year observed in the randomised Phase III pirfenidone studies (15%) and randomised Phase II and III nintedanib studies (21%) [2, 3]. Since discontinuation rates after 24 weeks for pirfenidone were 6–8% in the CAPACITY studies, it was estimated that nintedanib discontinuation rates after 24 weeks would be around 10–11%. However, it is possible that addition of nintedanib to ongoing pirfenidone treatment could increase the proportion of patients discontinuing due to TEAEs, since both pirfenidone and nintedanib are associated with increased risk of GI and hepatic AEs. Assuming 85% of the patients completed 24 weeks of combination treatment, a sample size of 80 patients would be expected to yield an actual completion rate of 77.2–92.8% using a 95% confidence interval.

References

1. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Date last updated: June 14 2010. Date last accessed: January 30 2018.

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3. Genentech. Product label: Full prescribing information - Esbriet®. http://www.gene.com/download/pdf/esbriet_prescribing.pdf. Date last updated: 2017. Date last accessed: January 26 2018.