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Serious adverse events in patients with idiopathic pulmonary fibrosis in the placebo arms of 6 clinical trials

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ABSTRACT

Background: Idiopathic pulmonary fibrosis (IPF) is a fatal interstitial lung disease characterized by irreversible loss of lung function and an unpredictable course of disease progression.
Methods: The safety data for patients with IPF who received placebo in 6 clinical trials were pooled to examine the categories and frequencies of serious adverse events (SAEs) in this population.
Results: In 1082 patients with IPF who received placebo, 673 SAEs were reported. Of these, 93 SAEs resulted in death (8.6% of patients). Respiratory-related conditions were the most frequently reported SAE (225 events, 16.33 per 100 patient-exposure years [PEY]), followed by infections and infestations (136 events, 9.87 per 100 PEY) and cardiac disorders (79 events, 5.73 per 100 PEY); these categories also had the most fatal outcomes (60, 10, and 10 deaths, respectively). The most frequently reported fatal respiratory-related SAEs were IPF and respiratory failure (38 and 11 patients, respectively), and the most frequently reported fatal infections and infestations and cardiac disorders were pneumonia (5 patients) and myocardial infarction (3 patients), respectively.
Conclusions: This pooled analysis has value as a comparator for safety in future studies of IPF and provides insights in the natural evolution of both IPF and common comorbidities.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a debilitating, progressive, fatal fibrotic lung disease of unknown etiology with a poor prognosis and no cure [1]. Patients with IPF experience irreversible decline in lung function, although rates of decline are highly variable [2–4]. The median survival for patients diagnosed with IPF was 2–3 years prior to the approval of antifibrotic therapies [4]. Disease progression in IPF is often accentuated by acute exacerbations, unpredictable periods of rapid lung function decline typified by diffuse alveolar damage [5]. Acute exacerbations, declines in percent predicted forced vital capacity (FVC), and respiratory-related hospitalizations are associated with high rates of short-term mortality [6–8]. Comorbidities, including cardiovascular disease and cardiovascular risk factors, are common in patients with IPF and are associated with poor outcomes [9–13].

The unpredictability of disease progression necessitates further investigation into the natural history of IPF. With the availability of antifibrotic therapies, long-term placebo-controlled studies in IPF are no longer feasible [14]. Except for the population of patients who are intolerant of antifibrotic therapies, patients enrolled in future long-term

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trials will likely receive study drugs as add-on treatment to an established antifibrotic therapy, and the trials will generate limited new information on the clinical behavior of the disease without treatment. Therefore, for studying the natural history of IPF, the placebo groups of previously completed randomized clinical trials serve as one of the best available data sources.

This analysis draws on the pooled safety data from the placebo arms of 6 randomized clinical trials in IPF sponsored by InterMune, Inc., and F. Hoffmann-La Roche Ltd. Three phase 3 clinical trials, ASCEND (Study 016; NCT01366209) and CAPACITY (Studies 004 and 006; NCT00287716 and NCT00287729), established the benefit of pirfenidone in delaying disease progression in patients with IPF [15,16]. The phase 3 GIPF-001 trial (NCT00047645), the phase 2 GIPF-002 trial (NCT00047658), and the phase 3 INSPIRE trial (GIPF-007; NCT00075998) did not support the efficacy of interferon-γ 1b in IPF [17–19]. Safety data from the placebo arms of these studies provide a large cohort of well-characterized patients with IPF followed in a controlled clinical setting [15–19].

This post hoc analysis summarizes the serious adverse events (SAEs) reported to the global safety database for 1082 patients who were diagnosed with IPF and randomized to the placebo arm in 6 randomized controlled trials. The characterization of the SAEs with the evolution and occurrence of comorbidities in these patients may benefit clinicians and investigators studying new IPF treatments and monitoring the safety of approved therapies.

2. Methods

2.1. Study design and population

Safety data from the placebo arms of 6 randomized clinical trials in patients with IPF were pooled to assess the pattern of SAEs and deaths over the full follow-up duration available in the global safety database for each trial. Three trials investigated interferon-γ 1b: GIPF-001, GIPF-002, and INSPIRE [17]. Three trials investigated pirfenidone: ASCEND and CAPACITY (Studies 004 and 006) [15,16].

In accordance with the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, SAEs were broadly defined as AEs that resulted in death, were life threatening, required prolonged hospitalization, resulted in persistent or significant disability or incapacity, or were medically significant as judged by the investigator. In ASCEND and CAPACITY, per protocol, elective surgical procedures that required hospitalizations and were scheduled for stable conditions, including lung transplant, were not recorded as SAEs.

SAEs from the placebo arms of these 6 trials were retrieved from a search of the global safety database in which they were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18.1. Types of SAEs were compared by MedDRA system organ class (SOC) and preferred terms recorded in the database. The global safety database tracked unique cases. Each case may consist of several events for the same patient, and each patient may have ≥1 case reported in the database, which is a potential source of overlap in reporting. Detailed patient narratives were not captured in the global safety database.

The clinical trials included in this analysis were conducted in accordance with the International Conference on Harmonisation Guidelines and the Declaration of Helsinki, as well as the relevant local legal and regulatory requirements where the trials were conducted. Written informed consent was obtained from all participating patients, and the approval of the ethics committee/institutional review board for each participating study site was obtained prior to initiating study procedures.

2.2. Statistical analysis

SAEs reported to the safety database across the 6 trials were described as the number of events and the number of events per 100 patients. Total exposure in patient-exposure years (PEY) was summed across the 6 studies using the following calculation for each patient who received placebo: (last dose date − first dose date + 1 day)/365.25 days. Event rates per 100 PEY were calculated as 100 × (total number of events)/(total exposure in PEY). Latency for SAEs was calculated using the therapy start date and the event onset dates retrieved from the database. The Kaplan-Meier method was used to estimate survival in each trial (excluding GIPF-002 due to the small study population and short study duration).

3. Results

3.1. Patients

A total of 1082 patients received placebo treatment in the 6 randomized controlled trials pooled in this analysis. The total exposure across all 6 trials was 1377.7 PEY.

The trials had generally similar study designs, but there were some key differences in the lung function test inclusion criteria and concomitant medications were excluded (Supplemental Table 1). Across the 6 trials, there were differences in the baseline % predicted FVC and baseline percent predicted diffusing capacity for carbon monoxide (DLCO) inclusion criteria. Two of the 3 interferon-γ 1b trials (GIPF-001 and GIPF-002) enrolled patients with baseline % predicted FVC of ≥50% and ≤90%, while INSPIRE enrolled patients with baseline % predicted FVC of ≥55% and ≤90%. Baseline % predicted DLCO of ≥25% was required for inclusion in 2 of 3 interferon-γ 1b trials (GIPF-001 and GIPF-002). INSPIRE required a baseline DLCO of ≥35%. In ASCEND, baseline pulmonary function inclusion criteria were % predicted FVC of ≥50% and % predicted DLCO of ≤90% and ≥30%; however, in CAPACITY, patients were required to have either a baseline % predicted FVC of ≥50% and ≤90% with % predicted DLCO of ≥35% or a % predicted DLCO of ≥35% and ≤90% with % predicted FVC of ≥50%. Patients in ASCEND were required to have a baseline forced expiratory volume in 1 s (FEV_1) to FVC ratio ≥0.80 to exclude patients with significant overlapping emphysema; no FEV_1/FVC ratio criterion was specified in the earlier trials. In all trials, only patients with IPF treated according to standard of care at the time of the trial were included, and all patients with other known explanations for interstitial lung disease (ILD), including sarcoidosis, hypersensitivity pneumonitis, and cancer, were excluded.

Among the concomitant medication exclusion and inclusion criteria, the most notable difference was in corticosteroid therapy. In the interferon-γ 1b trials, patients were permitted to receive stable corticosteroid therapy within specified dose ranges. In contrast, chronic corticosteroid use was not permitted in the CAPACITY trials; in ASCEND, it was permitted only to treat conditions other than IPF or an acute exacerbation of IPF for ≤28 days.

Despite some differences in the inclusion criteria, the patient demographics and baseline characteristics were largely similar across the trials. The patient populations were older (mean age, 63.0–67.8 years), and most patients were white (86.3%–98.8%) and male (53.3%–76.9%) (Supplemental Table 2). Across the 6 trials, the mean % predicted FVC (64.1%–76.2%) and mean % predicted DLCO (36.8%–47.4%) at baseline were mostly similar, reflecting similarities in the inclusion criteria. In the GIPF-001 and GIPF-002 populations, mean % predicted FVC and mean % predicted DLCO at baseline were somewhat lower than those in the other trials (FVC, 64.1%–67.6% vs 68.6%–76.2%; DLCO, 36.8%–40.1% vs 44.2%–47.4%). No formal statistical comparisons were made between baseline characteristics.

Although the capture methodologies varied slightly, including the MedDRA versions available at the times of the original studies, similarities were found in the underlying medical conditions in the patient populations. In GIPF-001 and GIPF-002 interferon-γ 1b trials, underlying musculoskeletal, gastrointestinal, cardiovascular, and head, eye, ear, nose, and throat disorders were reported in ≥50% of patients (Supplemental Table 3). In

Table 1
SAEs by SOC (per MedDRA definitions) reported in patients with IPF.

SAEs by SOC[a]	Combined placebo arms of pirfenidone and interferon-γ 1b trials N = 1082		
	Events, n (per 100 patients)	Incidence rate, events per 100 PEY[b]	Deaths, n
Respiratory, thoracic, and mediastinal disorders	225 (20.79)	16.33	60
Infections and infestations	136 (12.57)	9.87	10
Cardiac disorders	79 (7.30)	5.73	10
Gastrointestinal disorders	42 (3.88)	3.05	1
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	38 (3.51)	2.76	5
Nervous system disorders	32 (2.96)	2.32	1
General disorders and administration site conditions	24 (2.22)	1.74	5
Musculoskeletal and connective tissue disorders	19 (1.76)	1.38	0
Injury, poisoning, and procedural complications	13 (1.20)	0.94	0
Metabolism and nutrition disorders	13 (1.20)	0.94	0
Vascular disorders	12 (1.11)	0.87	0
Renal and urinary disorders	10 (0.92)	0.73	0
Psychiatric disorders	8 (0.74)	0.58	1
Hepatobiliary disorders	7 (0.65)	0.51	0
Surgical and medical procedures	4 (0.37)	0.29	0
Blood and lymphatic system disorders	3 (0.28)	0.22	0
Investigations	3 (0.28)	0.22	0
Reproductive system and breast disorders	2 (0.18)	0.15	0
Congenital, familial, and genetic disorders	1 (0.09)	0.07	0
Ear and labyrinth disorders	1 (0.09)	0.07	0
Eye disorders	1 (0.09)	0.07	0
All SAEs reported	673 (62.20)	48.85	93

IPF, idiopathic pulmonary fibrosis; MedDRA, Medical Dictionary for Regulatory Activities; PEY, patient-exposure years; SAE, serious adverse event; SOC, system organ class.
[a] Only SOCs that had SAEs (≥1) are listed.
[b] Incidence rates were calculated as 100 × (number of events)/(total exposure). Across the 6 studies, the total exposure was 1377.7 PEY.

Table 2
Respiratory, thoracic, and mediastinal disorder–related SAEs (by MedDRA-preferred term) reported in patients with IPF.

Respiratory, thoracic, and mediastinal disorder SAEs	Combined placebo arms of pirfenidone and interferon-γ 1b trials N = 1082		
	Events, n (per 100 patients)	Deaths, n	Latency range, days[a]
Idiopathic pulmonary fibrosis	108 (9.98)	38	21–780
Respiratory failure	28 (2.59)	11	13–573
Dyspnea	16 (1.48)	–	28–463
Acute respiratory failure	13 (1.20)	4	101–645
Hypoxia	9 (0.83)	2	92–631
Pulmonary embolism	7 (0.65)	1	97–538
Pulmonary fibrosis	7 (0.65)	1	33–645
Pneumothorax	5 (0.46)	–	177–621
Cough	4 (0.37)	–	21–470
Acute respiratory distress syndrome	3 (0.28)	1	247–497
Pneumonitis	3 (0.28)	–	44–504
Pneumothorax spontaneous	3 (0.28)	–	159–359
Bronchiectasis	2 (0.18)	–	444–539
Chronic obstructive pulmonary disease	2 (0.18)	–	52–522
Hemoptysis	2 (0.18)	–	235–475
Pleuritic pain	2 (0.18)	–	168–615
Pulmonary hypertension	2 (0.18)	–	117–567
Respiratory distress	2 (0.18)	–	101–458
Chronic respiratory failure	1 (0.09)	1	778
Respiratory arrest	1 (0.09)	1	165
All respiratory, thoracic, and mediastinal disorder SAEs	225 (20.79)	60	13–780

IPF, idiopathic pulmonary fibrosis; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse events.
[a] Latency was calculated from the date of receiving first study dose of placebo to the date of the event's onset.

INSPIRE and the pirfenidone trials, ≥50% of patients had underlying gastrointestinal disorders, metabolism and nutrition disorders, musculoskeletal and connective tissue disorders, vascular disorders, and respiratory, thoracic, and mediastinal disorders (Supplemental Table 4).

3.2. Serious adverse events

From the global safety database, 530 cases in patients who received placebo were identified, representing a total of 673 SAEs (48.85 per 100 PEY). The majority of SAEs were reported in 6 SOCs: respiratory, thoracic, and mediastinal disorders (225 events, 16.33 per 100 PEY); infections and infestations (136 events, 9.87 per 100 PEY); cardiac disorders (79 events, 5.73 per 100 PEY); gastrointestinal disorders (42 events, 3.05 per 100 PEY); neoplasms benign, malignant, and unspecified (including cysts and polyps; 38 events, 2.76 per 100 PEY); and nervous system disorders (32 events, 2.32 per 100 PEY) (Table 1). The

Table 3
Deaths by SOC in patients with IPF.

Deaths by SOC, n[a]	Placebo arms		
	Interferon-γ 1b trials n = 458	Pirfenidone trials n = 624	Combined pirfenidone and interferon-γ 1b trials N = 1082
Respiratory, thoracic, and mediastinal disorders	24	36	60
Cardiac disorders	5	5	10
Gastrointestinal disorders	1	0	1
General disorders and administration site conditions	5	0	5
Infections and infestations	5	5	10
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	3	2	5
Nervous system disorders	0	1	1
Psychiatric disorders	0	1	1
All deaths	43	50	93

IPF, idiopathic pulmonary fibrosis; SOC, system organ class.
[a] Only SOCs that had fatal events (≥1) are listed.

most frequently reported SAEs of the respiratory, thoracic, and mediastinal disorders were IPF (108 events), respiratory failure (28 events), and dyspnea (16 events) (Table 2). Among infections and infestations, the most frequently reported SAEs were pneumonia (60 events) and bronchitis (19 events); among cardiac disorders, they were myocardial infarction (13 events), coronary artery disease (10 events), and atrial fibrillation (9 events) (Supplemental Table 5). Among malignancies, the 2 most commonly reported SAEs were prostate cancer (7 events) and breast cancer (4 events).

Of all 673 SAEs, 93 resulted in death (6.75 per 100 PEY) (Table 1). Most deaths were reported in 3 SOCs: respiratory, thoracic, and mediastinal disorders (60 deaths, 4.36 per 100 PEY); infections and infestations (10 deaths, 0.73 per 100 PEY); and cardiac disorders (10 deaths, 0.73 per 100 PEY) (Table 3). The most frequent SAEs with a fatal outcome were IPF (38 deaths) and respiratory failure (11 deaths) (Table 4). The most frequently reported SAE with a fatal outcome among infections and infestations was pneumonia (5 deaths) and among cardiac disorders was myocardial infarction (3 deaths) (Supplemental Table 5).

Overall survival at 52 weeks was > 90% in 4 of 5 trials with sufficient data for survival analysis (Fig. 1); the median survival was not reached. Survival at 52 weeks was lowest in the GIPF-001 trial, but there were no clear differences between the populations in the other 2 interferon-γ 1b trials and the pirfenidone trials. However, no formal comparisons or adjustments for baseline factors were made.

4. Discussion

The combined placebo arms of past clinical trials in IPF present a cohort of well-characterized patients with IPF examined in a controlled clinical trial setting [15–19]. In this pooled analysis of safety data from 6 trials in IPF, the most frequently reported SAE (preferred term) was IPF, demonstrating the severity of the disease itself. IPF-related respiratory events, such as respiratory failure and dyspnea, were frequently reported, as were pneumonia and myocardial infarction.

Consistent with previous findings, the most frequent fatal SAEs were respiratory related, cardiovascular disorders, and infections. In previous reports, respiratory failure, both subacute and acute, comprised ≥50% of deaths in patients with IPF, while other leading causes of death included ischemic heart disease, heart failure, bronchogenic carcinoma, infections (including pneumonia), and pulmonary embolism [4,20]. In this analysis, more than half of all reported deaths were due to IPF or respiratory failure. Prostate cancer and breast cancer were the most frequently reported malignancies, consistent with the types of cancers experienced in this age group [21]. However, lung cancer is likely underrepresented in this cohort of patients, as patients with IPF have significantly greater risk of lung cancer compared with the general population, and computed tomography scans to confirm IPF diagnosis also serve to screen for lung cancer, an exclusion criterion for the 6 trials [22,23].

Differences between the study populations are an important consideration when drawing conclusions from this analysis. In the interferon-γ 1b trials, corticosteroids were permitted at a stable dose. At the time when the interferon-γ 1b trials were designed, corticosteroids were commonly prescribed for IPF, particularly in the case of acute exacerbations, despite a lack of strong evidence for efficacy [1]. In the pirfenidone trials, corticosteroids were not permitted in CAPACITY; they were permitted in a limited fashion to treat acute exacerbations and conditions other than IPF in ASCEND. Differences in methods of capturing medical history present challenges for direct comparisons, but there were no clear differences in the frequencies of underlying comorbid conditions observed between the patients who received placebo

Table 4
Respiratory, thoracic, and mediastinal disorder–related deaths (by preferred term) in patients with IPF.

Respiratory, thoracic, and mediastinal disorder deaths by SAE, n	Placebo arms		
	Interferon-γ 1b trials n = 458	Pirfenidone trials n = 624	Combined pirfenidone and interferon-γ 1b trials N = 1082
Idiopathic pulmonary fibrosis	12	26	38
Respiratory failure	6	5	11
Acute respiratory failure	3	1	4
Hypoxia	1	1	2
Pulmonary embolism	1	0	1
Pulmonary fibrosis	0	1	1
Acute respiratory distress syndrome	0	1	1
Chronic respiratory failure	1	0	1
Respiratory arrest	0	1	1
All respiratory, thoracic, and mediastinal disorder deaths	24	36	60

IPF, idiopathic pulmonary fibrosis; SAE, serious adverse event.

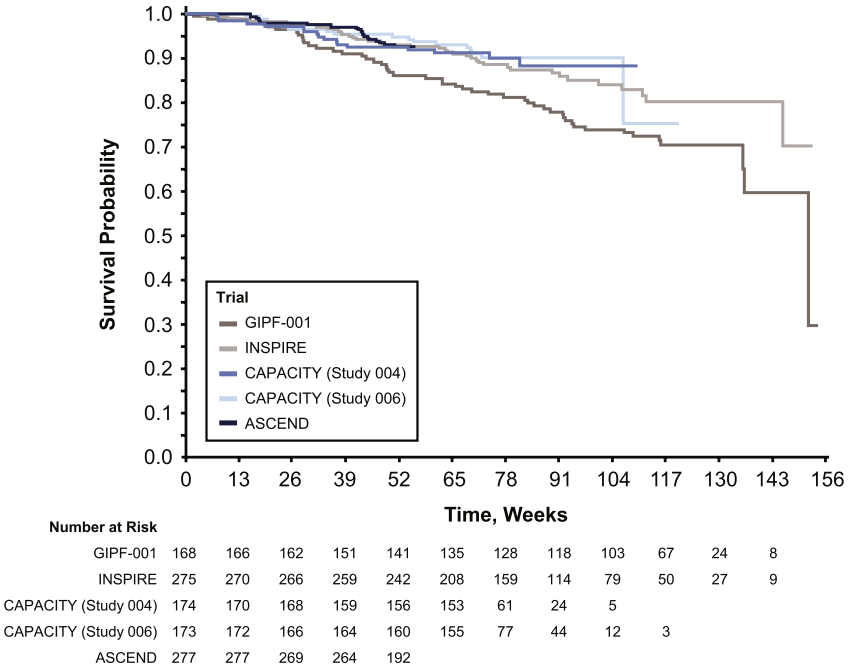

Fig. 1. Kaplan-Meier survival curve for patients who received placebo in the interferon-γ 1b and pirfenidone trials. The GIPF-002 trial was not included in the Kaplan-Meier analysis due to insufficient data.

in the 3 older interferon-γ 1b trials and those in the 3 more recent pirfenidone trials. The diagnosis of ILDs has evolved since the initiation of the interferon-γ 1b trials; patients with no other known explanations for ILD at the time might not be diagnosed with IPF in present clinical practice [24,25].

This study has several limitations for its implications in day-to-day clinical practice in IPF. The selection process used in choosing the clinical trial populations enforced a selection against conditions that may be common and relevant among patients in real-world settings. The trials excluded patients with prior lung disease, unstable cardiovascular disease, or diabetes and baseline pulmonary hypertension, and the trials had different durations of follow-up. The CAPACITY and interferon-γ 1b trials may have included a number of patients with overlapping emphysema, which could have influenced the incidence of SAEs. Relevant risk factors for mortality and SAEs were not explored in this analysis, such as non-SAE pulmonary hypertension. Additionally, these patients represent a subset of the IPF population with less advanced disease, low mortality over 1 year, and who were more likely to participate in clinical trials. During clinical trials, the global safety database captures only SAEs and AEs of special interest; therefore, non-SAEs that may provide a more complete picture of the clinical course of IPF could not be included in this analysis. Details on any individual case in the global safety database are limited by what was recorded at the time the investigator reported the case. The global safety database captured SAE cases, and potential overlap in reporting ≥1 SAE occurring in the same patient limits the ability to compare frequencies of potentially related SAEs.

These pooled safety data from a large cohort of well-characterized patients who received placebo in randomized clinical trials provide information on comorbidities. These data offer insights into the natural history of IPF. In future randomized clinical trials in IPF in which placebo arms with large enrolments are no longer feasible, these data may help guide trial evaluation and design.

Conflicts of interest

W. Wuyts has received grants from InterMune and has served as a speaker for Bayer, Boehringer Ingelheim, and Roche.

D. Antin-Ozerkis has received grants from Boehringer Ingelheim, Fibrogen, Genentech, and Promedior; all grants were paid to her institution.

J.T. Huggins has received grants from Boehringer Ingelheim, Celgene, Gilead, and Roche/Genentech.

P.P. LaCamera has served on advisory boards for Boehringer Ingelheim and InterMune/Roche/Genentech.

P. Spagnolo serves as a consultant for PPM Services S.A.; has served as a consultant for InterMune/Roche/Genentech, Santhera Pharmaceuticals, and Zambon; has served on scientific advisory boards for Boehringer Ingelheim, Galapagos, and Zambon; and has been a lecturer at symposia organized by Boehringer Ingelheim, InterMune/Roche/Genentech, and Novartis; P. Spagnolo's wife is an employee of Novartis.

M. Vašáková has served as a consultant, speaker, and advisory board member for Boehringer Ingelheim and InterMune/Roche.

M.S. Wijsenbeek has received grants and speaker and advisory board fees from Boehringer Ingelheim and InterMune/Roche and advisory board fees from Galapagos; all grants and fees were paid to her institution.

B. Polman is an employee of Genentech, Inc.

K.-U. Kirchgaessler is an employee of F. Hoffmann-La Roche Ltd.

M.B. Scholand has served on advisory boards for Boehringer Ingelheim and InterMune/Roche/Genentech.

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W.W. has received grants from InterMune and has served as a speaker for Bayer, Boehringer Ingelheim, and Roche. **D.A.-O.** has received grants from Boehringer Ingelheim, Fibrogen, Genentech, and Promedior; all grants were paid to her institution. **J.T.H.** has received grants from Boehringer Ingelheim, Celgene, Gilead, and Roche/

Genentech. **P.P.L.** has served on advisory boards for Boehringer Ingelheim and InterMune/Roche/Genentech. **P.S.** serves as a consultant for PPM Services S.A.; has served as a consultant for InterMune/Roche/Genentech, Santhera Pharmaceuticals, and Zambon; has served on scientific advisory boards for Boehringer Ingelheim, Galapagos, and Zambon; and has been a lecturer at symposia organized by Boehringer Ingelheim, InterMune/Roche/Genentech, and Novartis; P.S.'s wife is an employee of Novartis. **M.V.** has served as a consultant, speaker, and advisory board member for Boehringer Ingelheim and InterMune/Roche. **M.S.W.** has received grants and speaker and advisory board fees from Boehringer Ingelheim and InterMune/Roche and advisory board fees from Galapagos; all grants and fees were paid to her institution. **B.P.** is an employee of Genentech, Inc. **K.-U.K.** is an employee of F. Hoffmann-La Roche Ltd. **M.B.S.** has served on advisory boards for Boehringer Ingelheim and InterMune/Roche/Genentech.

Data sharing

Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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Appendix A. Supplementary data

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