EUROPEAN RESPIRATORY journal

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

Phase 2 trial to assess lebrikizumab in patients with idiopathic pulmonary fibrosis

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Please cite this article as: Maher TM, Costabel U, Glassberg MK, *et al*. Phase 2 trial to assess lebrikizumab in patients with idiopathic pulmonary fibrosis. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.02442-2019).

Title: Phase 2 trial to assess lebrikizumab in patients with idiopathic pulmonary fibrosis

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Submission to: *European Respiratory Journal*

Word limits/counts:

Take-home message: 256 characters (for social media), current=**255**

Abstract: 250 words, current=**254**

Manuscript: 3000 words (original research), current=**3405**; 40 references, current=**29**

Figures/tables: 8 (current=**7**)

Take-home message:

This phase 2 RCT found no benefit in %FVC decline over 52 weeks in patients with IPF for lebrikizumab vs. placebo as monotherapy (n=78 vs. 76) or in combination with pirfenidone (n=174 vs. 177); pirfenidone treatment was consistent with previous results.

Abstract

This phase 2, randomised, double-blind, placebo-controlled trial evaluated the efficacy and safety of lebrikizumab, an interleukin-13 monoclonal antibody, alone or with background pirfenidone therapy, in patients with idiopathic pulmonary fibrosis (IPF).

Patients with IPF aged ≥40 years with % predicted forced vital capacity (%FVC) 40%–100% and diffusing capacity for carbon monoxide 25%–90% and who were treatment-naive (Cohort A) or receiving pirfenidone (2403 mg/day; Cohort B) were randomised 1:1 to receive lebrikizumab 250 mg or placebo subcutaneously every 4 weeks. The primary endpoint was annualised rate of %FVC decline over 52 weeks.

In Cohort A, 154 patients were randomised to receive lebrikizumab (n=78) or placebo (n=76). In Cohort B, 351 patients receiving pirfenidone were randomised to receive lebrikizumab (n=174) or placebo (n=177). Baseline demographics were balanced across treatment arms in both cohorts. The primary endpoint (annualised rate of %FVC decline) was not met in Cohort A (lebrikizumab vs. placebo, −5.2% vs. −6.2%; *P*=0.456) or Cohort B (lebrikizumab vs. placebo, −5.5% vs. −6.0%; *P*=0.557). In Cohort B, a non-statistically significant imbalance in mortality favouring combination therapy was observed (hazard ratio, 0.42 [95% CI, 0.17–1.04]). Pharmacodynamic biomarkers indicated lebrikizumab activity. The safety profile was consistent with that in previous studies of lebrikizumab and pirfenidone as monotherapies.

Lebrikizumab alone or with pirfenidone was not associated with reduced %FVC decline over 52 weeks despite evidence of pharmacodynamic activity. Lebrikizumab was well tolerated with a favourable safety profile. These findings suggest that blocking IL-13 may not be sufficient to achieve a lung function benefit in patients with IPF.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive, irreversible, fibrosing lung disease with an unpredictable rate of decline, a poor prognosis and a 10-year survival rate of ≤15% [1-3]. Pirfenidone is 1 of 2 approved antifibrotic therapies for IPF. Pirfenidone slows lung function decline as measured by % predicted forced vital capacity (FVC), improves progression-free survival (PFS) and reduces all-cause mortality [4-6]. However, little benefit has been shown for dyspnoea, quality of life or other clinically meaningful outcomes in the pivotal trials [4, 5]. As a result, there remains an unmet need for identifying new treatments that may offer additional clinical benefit to patients with IPF.

Interleukin-13 (IL-13) is a potent activator of fibroblasts, promoting extracellular matrix synthesis with potential pathogenic roles in fibrosis [7-10]. In mouse models, IL-13 deficiency or defective IL-13 signalling reduced lung fibrosis, whereas overexpression of IL-13 increased lung fibrosis [11-15]. In lung biopsy samples from patients with IPF, expression levels of IL-13, IL-13 receptors and IL-13 target genes were increased compared with normal controls [16, 17]. In bronchoalveolar lavage fluid from patients with IPF, IL-13 levels were elevated compared with normal controls, and IL-13 levels were negatively correlated with key measures of lung function, such as % predicted FVC and % predicted diffusing capacity for carbon monoxide (DL_{CO}), suggesting pathogenic functions of IL-13 in patients with IPF [18]. C-C motif ligand 18 (CCL18) and periostin are IL-13 pathway biomarkers with levels that are elevated in IPF and are associated with lung function decline or death [19].

Lebrikizumab is a humanised monoclonal antibody that specifically binds soluble IL-13 to neutralize its activity and inhibit subsequent downstream signalling [20]. The RIFF study was designed initially to evaluate lebrikizumab as monotherapy and subsequent to the approval of pirfenidone, a second cohort study was added to evaluate lebrikizumab combination with pirfenidone for the treatment of patients with IPF.

Methods

Study design

RIFF (NCT01872689) was a randomised, multicentre, double-blind, placebo-controlled study of lebrikizumab vs. placebo in patients with IPF. RIFF was initially designed as a time-to-event trial to assess the benefit of lebrikizumab on PFS. (See supplemental methods for sample size calculations, randomisation, blinding and dosing administration.)

After the US Food and Drug Administration approved pirfenidone in October 2014, the RIFF protocol was amended in January 2015 to limit the number of patients (total 150 patients) and duration of blinded monotherapy assessment (52 weeks), designated as Cohort A. Cohort B was added to assess the benefit of lebrikizumab vs. placebo in patients receiving background pirfenidone therapy. The 2 cohorts were independent and enrolled sequentially. Patients entered a 28-day screening period after providing written informed consent.

In Cohort A, patients were randomised 1:1 to receive lebrikizumab 250 mg monotherapy or placebo every 4 weeks (q4w) for ≥52 weeks (figure 1A). Study treatment was administered via subcutaneous injection, with the first injection occurring at randomisation (Day 1, Visit 2). After the placebo-controlled period, patients who did not discontinue received open-label lebrikizumab treatment for 52 weeks. All patients were followed for 18 weeks after last dose of study treatment (safety follow-up).

In Cohort B, patients were randomised 1:1 to either lebrikizumab 250 mg or placebo q4w in combination with pirfenidone (≤2403 mg/day) for 52 weeks (figure 1B). Pirfenidone-naive patients initiated a run-in period (4–6 weeks) to allow pirfenidone titration to 2403 mg/day (per prescribing information), the highest dose tolerated or recommended dose per country-specific guidelines [21]. Study treatment and safety follow-up matched those of Cohort A.

This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. Approval was obtained from all institutional review boards prior to study initiation. (See supplemental methods for ethics approvals.)

Patients

Key eligibility criteria included age ≥40 years, diagnosis of IPF per the 2011 international guidelines ≤5 years before screening (confirmed by central review of high-resolution computed tomography during screening period or ≤12 months prior to screening, with multidisciplinary evaluation if needed), stable (<10% difference in FVC [L] between screening and randomisation), % predicted FVC ≥40% and ≤100%, % predicted DL_{CO} ≥25% and ≤90% and 6-minute walk distance (6MWD) ≥100 m [3]. In Cohort A, patients received no background IPF therapy for ≥4 weeks prior to randomisation and throughout the placebo-controlled period. In Cohort B, patients received pirfenidone ≤2403 mg/day for ≥4 weeks prior to randomisation and throughout the placebo-controlled period. (See supplemental methods for key exclusion criteria.)

Assessments

Serum chemokine CCL13, CCL18 and periostin, biomarkers of the IL-13 pathway, were measured at baseline and Weeks 4, 24 and 52. In the prior development programme of lebrikizumab in asthma, antibodies against phospholipase B-like protein 2 (PLBL2), a process-related protein impurity, were detected in some patients; no association between immunogenicity and safety was observed [22]. Blood samples for detecting and characterising anti-drug antibodies (ADAs) to lebrikizumab and PLBL2 were collected at baseline and regular intervals to assess immunogenicity. (See supplemental methods for additional biomarker assessment and immunogenicity details.)

Adverse events (AEs), serious AEs (SAEs) and AEs of special interest (AESIs) were assessed during the 52-week placebo-controlled period in both cohorts and during the lebrikizumab exposure period (from first dose of lebrikizumab until the end of safety follow-up) in Cohort A. AEs were reported by the investigator and coded per Medical Dictionary for Regulatory Activities terms (version 20.1); no adjudication was performed. AESIs included

anaphylactic reactions, local injection-site reactions, infections and malignancies. AESIs related to pirfenidone as identified in the phase 3 clinical trials included photosensitivity or rash, gastrointestinal-related AEs (e.g., nausea, diarrhoea, vomiting) and elevated liver enzyme levels [4, 5].

Endpoints and analyses

The primary endpoint was the annualised rate of decline in % predicted FVC through Week 52 in the ITT population, which was compared across treatment arms with use of a random slope model at a 0.05 two-sided significance level. From the model, least squares means for the annualised rate of decline in each treatment arm included all FVC measurements collected at baseline, Weeks 1, 4, 12, 24, 36, 44 and 52, and the difference between the two treatment arms was provided with 95% CIs. No imputation for missing results because of death or other reasons were implemented. Missing data was handled by the model under the missing-at-random assumption (i.e., assuming that % predicted FVC decreases linearly over time).

Secondary efficacy endpoints in Cohort A and Cohort B included PFS, annualised rates of decline in % predicted DL_{CO} and 6MWD at Week 52, annualised rate of change from baseline in A Tool to Assess the Quality of Life in IPF (ATAQ-IPF) total score at Week 52 and time from randomisation to death from any cause [23]. The Borg Category Ratio 10 Scale (Borg scale) was collected as an exploratory endpoint. In Cohort A, the Saint George Respiratory Questionnaire was assessed. In Cohort B, time-to-event endpoints were also evaluated, including time to respiratory-related hospitalisation, acute exacerbation or death, ≥10% absolute decline in % predicted FVC or death and ≥15% absolute decline in DL_{CO} or death. Kaplan-Meier estimates, log-rank tests stratified by baseline lung function for *P* values and Cox regression models to estimate hazard ratios (HRs) and 95% CIs were used to compare time-to-event endpoints.

All patients who received ≥1 dose of study drug and had ≥1 non-missing pharmacokinetic observation were included in the pharmacokinetic-evaluable population. Changes from baseline levels for pharmacodynamic biomarkers were evaluated in the ITT population.

Results

Patients

In Cohort A, 325 patients were screened at 156 sites in 13 countries (figure 2) between October 2012 and April 2015. Of 154 patients randomised (screen fail rate, 53%), 76 patients received placebo and 78 received lebrikizumab; 114 patients (74%) completed the placebo-controlled period. Of patients who completed the placebo-controlled period, 108 continued and received open-label lebrikizumab, and 64 of these patients (59%) completed the open-label period. In Cohort B, 623 patients were screened between May 2015 and August 2016. Of 351 randomised receiving background pirfenidone therapy (screen fail rate, 44%), 174 patients received lebrikizumab and 177 received placebo; 265 patients (75%) completed the placebo-controlled period. The most common reasons for discontinuation in both cohorts were withdrawal by patient, death and AEs.

The demographic profiles of the patients enrolled in the 2 treatment arms of Cohort A and Cohort B were comparable (table 1; supplemental table S1). The majority of patients were male (83% and 81% in Cohorts A and B, respectively) and white (82% and 86%). The median (range) age was 70 (51–88) years in Cohort A and 69 (50–86) years in Cohort B.

Baseline disease characteristics, including % predicted FVC and % predicted DL_{CO}, were comparable between treatment arms in both cohorts. Most patients (≥93%) had ≥1 medical history finding, including both active comorbid conditions and inactive past conditions. The most common targeted medical history conditions (≥20% in either arm) in Cohort A were gastro-oesophageal reflux disease (GERD; lebrikizumab, 39.7% vs. placebo,

42.1%), arthritis (19.2% vs. 26.3%), coronary artery disease (29.5% vs. 15.8%), type 2 diabetes mellitus (19.2% vs. 25.0%) and pneumonia (20.5% vs. 11.8%). In Cohort B, the most common conditions were GERD (lebrikizumab, 52.3% vs. placebo, 54.8%), coronary artery disease (24.1% vs. 20.9%) and arthritis (19.5% vs. 24.9%). Most patients (≥98%) in both treatment arms of both cohorts received ≥1 concomitant medication during the placebo-controlled period (supplemental table S2). The most common (≥50%) concomitant medications in any treatment arm were proton-pump inhibitors, statins, steroids and salicylates.

Efficacy

The primary endpoint was not met for either cohort (figure 3). No difference was observed in the annualised rate of decline in % predicted FVC over 52 weeks in either Cohort A (lebrikizumab, −5.2% [SEM, 0.93] vs. placebo, −6.2% [0.93]; difference, 0.98% [1.31]; *P*=0.456) or Cohort B (lebrikizumab, −5.5% [0.60] vs. placebo, −6.0% [0.61]; difference, 0.50% [0.85]; *P*=0.557).

In Cohort A, no effect on mortality was observed, with other secondary endpoints showing numerical trends that favoured lebrikizumab (table 2). A numerical imbalance in mortality favouring lebrikizumab plus pirfenidone treatment was observed in Cohort B (HR, 0.42 [95% CI, 0.17–1.04]; *P*=0.053) (figure 4). The small difference in event rate (7 deaths for lebrikizumab plus pirfenidone; 15 deaths for placebo plus pirfenidone) was driven by more deaths due to acute exacerbations in the placebo plus pirfenidone arm of Cohort B. A similar trend was observed in favour of lebrikizumab for time to first acute exacerbation or death in Cohort B (HR, 0.61 [95% CI, 0.29–1.25]) (supplemental figure S1). No treatment benefit was observed for other secondary endpoints in Cohort B (table 2).

Exploratory biomarker analyses

Baseline levels of serum CCL13, CCL18 and periostin were comparable between the arms within each cohort (supplemental table S3). Decreases in all 3 biomarkers were observed in the

lebrikizumab-treated patients for both cohorts compared with their respective placebo or pirfenidone-treated controls, suggesting that lebrikizumab is active to block a component of these circulating biomarkers that is downstream of IL-13 (supplemental figure S2). The level of biomarker modulation between patients treated with lebrikizumab was consistent regardless of background pirfenidone treatment.

Pharmacokinetics

Following subcutaneous administration of lebrikizumab 250 mg q4w with or without pirfenidone, the observed mean trough concentrations were similar at Week 4 (supplemental table S4). The observed mean trough concentrations increased ≈2-fold from Week 4 to Week 52 for both cohorts. The mean (SD) half-life estimates of lebrikizumab were similar across both cohorts (23.5 [5.36] days for Cohort A and 21.9 [4.79] days for Cohort B). Assessment of the exposure relationship to FVC change across 52 weeks in Cohort B suggested the response was not strongly associated with exposure (supplemental figure S3). No exposure relationships were identified in patients that were hospitalised for a respiratory cause compared with those who were not, at Weeks 24, 36, and 52 or for patients that later died.

Safety

The duration of lebrikizumab treatment was similar between Cohort A and Cohort B (supplemental table S5). The total number of AEs was comparable between treatment arms in both cohorts (table 3). During the placebo-controlled period, AEs were reported in 75 (96.2%) and 71 (93.4%) patients in the lebrikizumab and placebo arms of Cohort A, respectively, and 158 (90.8%) and 171 (96.6%) in the lebrikizumab and placebo arms of Cohort B, respectively. The frequencies of common AEs were generally similar between treatment arms in Cohort A and were similar or lower in the lebrikizumab arm than in the placebo arm of Cohort B (supplemental table S6). Photosensitivity reactions were less frequent in the lebrikizumab arm

than in the placebo arm of Cohort B (3.4% vs. 12.4%, respectively). During the lebrikizumab exposure period, 96.9% of patients in Cohort A experienced ≥1 AE (supplemental table S7).

In the placebo-controlled period, 23 (29.5%) and 19 (25.0%) patients reported SAEs in the lebrikizumab and placebo arms of Cohort A, respectively; 56 (32.2%) and 47 (26.6%) reported SAEs in the lebrikizumab and placebo arms of Cohort B, respectively (table 3). Treatment-related SAEs (investigator assessment) were reported in 2 patients who received lebrikizumab and 1 who received placebo in Cohort A and 3 who received lebrikizumab and 6 who received placebo in Cohort B with background pirfenidone. The most common SAEs (≥2% of patients in either arm in either cohort) were IPF (worsening or exacerbation as reported by the investigator), respiratory tract infection and pneumonia. In Cohort A, pneumothorax, pulmonary embolism and cardiac failure SAEs also occurred in ≥2% of patients (in either arm). During the lebrikizumab exposure period, 57 patients (43.8%) in Cohort A experienced a total of 92 SAEs, of which 3 had treatment-related SAEs as assessed by the investigator). Incidences of AESIs were comparable between treatment arms in both cohorts (table 3). No AEs met Sampson's criteria for anaphylaxis.

In Cohort A, 19 patients died during the study; 15 deaths occurred during the lebrikizumab exposure period (supplemental table S8). During the placebo-controlled period, 3 patients (3.8%) in the lebrikizumab arm and 3 (3.9%) in the placebo arm died. Nine deaths occurred during open-label lebrikizumab treatment and 4 during safety-follow-up. The most common cause of death in Cohort A was IPF (10 patients). Three deaths in Cohort A were considered related to study drug by the investigator: IPF (during safety follow-up following double-blind placebo treatment), acute respiratory failure (5 days after receiving open-label lebrikizumab following double-blind placebo treatment) and pulmonary embolism (during the placebo-controlled period following lebrikizumab treatment).

In Cohort B, 29 patients died; 22 deaths occurred during the placebo-controlled period: 9 (5.2%) and 13 (7.3%) in the lebrikizumab and placebo arms, respectively (supplemental

table S8). Seven deaths in Cohort B occurred during safety-follow-up. IPF was the most common cause of death in both lebrikizumab and placebo arms (5 and 8 patients, respectively). Of 29 deaths in Cohort B, 1 in the placebo arm with background pirfenidone (due to IPF, during the placebo-controlled period) was considered related to study drug by the investigator.

Lebrikizumab ADAs and PLBL2 antibodies were detected in 5.7% (14 of 247) and 24.7% (42 of 170), respectively, of lebrikizumab-treated patients in both cohorts. The median time to onset of lebrikizumab ADAs was ≈12 weeks. There was no evidence to suggest an adverse impact the presence of positive anti-lebrikizumab antibodies or anti-PLB2 antibodies on safety profiles of patients who received lebrikizumab treatment (data not shown).

Discussion

RIFF failed to meet the primary endpoint in patients with IPF. Lebrikizumab monotherapy (Cohort A) was not associated with a treatment benefit on lung function, mortality or other patient-relevant outcomes. Addition of lebrikizumab to background pirfenidone therapy (Cohort B) was also not associated with a treatment benefit on lung function. The overall rates of FVC decline observed in Cohorts A and B were similar despite the use of background pirfenidone in Cohort B. However, direct comparisons cannot be made as they were conducted as separate studies in different trial eras under a single protocol. In Cohort B, a non-statistically significant imbalance in mortality favouring combination therapy was observed (HR, 0.42 [95% CI (0.17–1.04)]). The difference in event rate was driven by more deaths due to acute exacerbations in patients who received placebo with background pirfenidone. A similar trend favouring lebrikizumab was observed for time to acute exacerbation or death in cohort B (HR, 0.61 [95% CI (0.29–1.25)]). Reduced mortality is an important outcome in IPF. In the phase 3 trials of pirfenidone and nintedanib, which led to their approval to treat IPF, the effect on mortality was reported across individual studies and in pooled analyses combining phase 3 data for each therapy [4-6, 24, 25]. A mortality benefit was not observed for nintedanib in either

individual trial nor in the pooled analysis [24, 25]. In the pirfenidone phase 3 studies, a mortality benefit was observed in 1 of 3 phase 3 trials and in the pooled analysis [4-6]. Thus, the observed limited reduction in the rate of acute exacerbations and subsequent death of patients treated with combination therapy may warrant further investigation, as this study was powered to show only lung function changes.

Other clinical trials in IPF that have assessed IL-13 antibodies have also demonstrated a lack of efficacy in this patient population, suggesting that IL-13 may not be an appropriate therapeutic target in IPF. A phase 2 randomised, double-blind, placebo-controlled trial that assessed the safety, tolerability and change in FVC at 52 weeks of the anti–IL-13 QAX576 in 60 patients with IPF was terminated [26]. A phase 2, randomised, double-blind, placebo-controlled trial that assessed change in % predicted FVC at 72 weeks of the anti–IL-13 tralokinumab in 302 patients with IPF was terminated due to lack of efficacy after the interim analysis [27]. A phase 2, randomised, double-blind, placebo-controlled trial that assessed change in % predicted FVC at 52 weeks of the anti–IL-13/IL-4 SAR156597 in 325 patients with IPF showed no significant difference in the primary efficacy endpoint [28]. However, a similar trend towards a decrease in acute exacerbations was reported in Cohort B. The reported rates of acute exacerbations in the IPF clinical trial setting is variable (4-28%) likely due to differences in study population, acute exacerbation definition and statistical methods [29]. In Cohort B, the event rate in the lebrikizumab plus pirfenidone arm was 2.9% (5 acute exacerbations) vs. 6.2% (11) in placebo plus pirfenidone arm (HR 0.45 [0.16, 1.31]; $P = 0.1346$). Although the overall number of acute exacerbations was low and the difference in the rate of acute exacerbations did not reach statistical significance, it is interesting to note that there were no deaths associated with acute exacerbations in the lebrikizumab plus pirfenidone arm, while 7 of 11 patients in the placebo plus pirfenidone arm died, consistent with reported rates of mortality post-acute exacerbation ≥ 50%. While these findings are similar to results reported in the SAR15697 trial targeting IL-4

and IL-13, there was no evidence of a treatment difference between lebrikizumab and placebo in Cohort A (HR 1.21 [0.41–3.61]; *P* = 0.73).

The pharmacokinetics (e.g., half-life estimates) and pharmacodynamics of lebrikizumab were similar in both cohorts, suggesting that background pirfenidone therapy did not impact lebrikizumab concentrations or activity. Pharmacodynamic measures supported lebrikizumab biological activity, both alone and in the presence of background pirfenidone therapy. Furthermore, efficacy/response relationships were generally flat across endpoints and did not suggest that increased dosing would have led to greater improvements in efficacy endpoints.

This study has several limitations. Each independent cohort was powered to detect differences in lung function between lebrikizumab and placebo treatment arms, but not differences in other outcomes. The approval of two antifibrotic therapies in late 2014 contributed to early patient discontinuation in Cohort A, which limited the amount of data captured to evaluate lebrikizumab as monotherapy. During the recruitment phase of Cohort A, 168 patients (51.6%) screened did not meet eligibility criteria similar to other anti-IL-13 trials executed between 2012 and 2016. It has been suggested that many of the patients referred to the anti-IL-13 trials may have been screening failures from the large phase 3 trials completing at that time and thus may not reflect the real-world population or populations studied in the prior phase 3 trials. In contrast, FVC and DL_{CO} measurements used standardised equipment, training and efforts with central over-read; thus, standardisation issues did not likely contribute to the lack of observed effect.

Lebrikizumab as monotherapy and in combination with pirfenidone was well tolerated, with a favourable safety profile, consistent with those reported for lebrikizumab and pirfenidone individually in phase 3 clinical trials [4, 5, 31]. The incidence of lebrikizumab or PLBL2 antibodies in both lebrikizumab- and placebo-treated patients did not appear to affect pharmacokinetics or safety.

In conclusion, lebrikizumab monotherapy or in combination with background pirfenidone therapy did not reduce lung function decline or provide other clinically significant benefits in patients with IPF.

Acknowledgments

We thank the patients and their families who participated in this study. The RIFF study was funded by F. Hoffmann-La Roche Ltd. and Genentech, Inc. We thank Becca Sheng of Genentech, Inc. for contributions to the pharmacodynamics analysis. Support for third-party writing assistance, furnished by Christine Gould, PhD, of Health Interactions, Inc., was provided by F. Hoffmann-La Roche Ltd.

Data sharing statement

Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). 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).

Author contributions

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; all authors contributed substantially to the study design, the data analysis and interpretation and the writing of the manuscript.

Conflicts of interest

T.M.M. has received research funding from GlaxoSmithKline and UCB via his institution; has served as a consultant and speaker for Apellis, AstraZeneca, Bayer, Blade Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Galapagos, GlaxoSmithKline, Indalo, Novartis, Pliant, ProMetic, Respivnat, Roche, Samumed and UCB.

U.C. has served as a member of a study adjudication committee for Gilead; has served as a consultant and speaker for Bayer, Boehringer Ingelheim and InterMune/Roche; has received grants from Boehringer Ingelheim and InterMune and has served as a consultant for Centocor, Fibrogen, Gilead, GlaxoSmithKline, UCB Celltech and Biogen.

M.K.G. was a member of the ASCEND study steering committee; has served as a consultant for Bellerophon, Boehringer Ingelheim, Bristol Myers Squibb, InterMune, RedX Pharma and Roche and has received research funding from Genentech/Roche.

Y.K. has received research funding from the Ministry of Health, Labour and Welfare, Japan; has served as a consultant for Genentech and has served as a consultant and speaker for Asahi Kasei, Boehringer Ingelheim, Eisai, Janssen, Kyorin, Mitsubishi Tanabe Pharma, Novartis and Shionogi.

T.O. has received research funding from Boehringer Ingelheim and the Ministry of Health, Labour and Welfare, Japan and has served as a consultant or speaker for Asahi Kasei, Boehringer Ingelheim, Eisai, Nitto Denko, Shionogi and Toray.

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

D.K., M.H., J.O., M.N. and P.B. are employees of Genentech, Inc.

J.J.S. was a member of the ASCEND study steering committee; has served on a scientific advisory board and received research funding from InterMune; served as a consultant to Boehringer Ingelheim and Roche; has received honoraria from Genentech.

Support statement

This study and manuscript were sponsored by F. Hoffmann-La Roche Ltd. and Genentech, Inc. The sponsor contributed to study design, data collection, data analysis, data interpretation, and writing of the report.

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Tables and figures

TABLE 1. Baseline demographics and clinical characteristics

Characteristic[#]	Cohort A			Cohort B		
	Lebrikizumab (n=78)	**Placebo (n=76)**	**All patients (N=154)**	**Lebrikizumab + pirfenidone (n=174)**	**Placebo + pirfenidone (n=177)**	**All patients (N=351)**
Age, years	70 (51–88)	69 (52–84)	70 (51–88)	69 (52–85)	69 (50–86)	69 (50–86)
Male, n (%)	65 (83.3)	63 (82.9)	128 (83.1)	137 (78.7)	147 (83.1)	284 (80.9)
White, n (%)	66 (84.6)	60 (78.9)	126 (81.8)	151 (86.8)	149 (84.2)	300 (85.5)
Time since diagnosis, years	0.92 (0.1–5.0)	1.53 (0.1–4.5)	1.07 (0.1–5.0)	1.51 (0.1–4.9)	1.54 (0.1–5.1)	1.54 (0.1–5.1)
FEV_1/FVC ratio	0.80 (0.6–0.9)	0.81 (0.6–1.0)	0.81 (0.6–1.0)	0.81 (0.7–1.0)	0.82 (0.7–1.0)	0.82 (0.7–1.0)
FVC, % predicted	73.0 (38.0–98.8)	72.8 (39.0–99.4)	73.0 (38.0–99.4)	71.5 (42.8–101.2)	73.4 (39.7–98.3)	72 (39.7–101.2)
DL_{CO}, % predicted	41.7 (22.3–73.6)	40.9 (25.0–67.9)	41.1 (22.3–73.6)	43.0 (12.9–71.3)	43.0 (19.5–84.0)	43.0 (12.9–84.0)
ATAQ-IPF total score[¶]	70.5 (34–114)	69.0 (34–119)	70.0 (34–119)	71.0 (36–117)	70.0 (34–118)	70.0 (34–118)
HRCT UIP diagnosis, n (%)						
n	78	75	153	174	177	348
Definite UIP	71 (91.0)	70 (93.3)	141 (92.6)	142 (81.6)	148 (83.6)	287 (82.6)
Possible UIP	7 (9.0)	5 (6.7)	12 (7.8)	28 (16.1)	28 (15.8)	56 (16.0)
Inconsistent with UIP	0	0	0	4 (2.3)	1 (0.6)	5 (1.4)
Surgical biopsy, n (%)						

n	78	76	154	172	176	348
Definite UIP	31 (39.7)	24 (31.6)	55 (35.7)	61 (35.5)	54 (30.7)	115 (33.0)
Probable UIP	5 (6.4)	11 (14.5)	16 (10.4)	17 (9.9)	8 (4.5)	25 (7.2)
Possible UIP	0	0	0	0	0	0
Not UIP	0	0	0	0	0	0
NA	42 (53.8)	41 (53.9)	83 (53.9)	94 (54.7)	114 (64.8)	208 (59.8)

ATAQ-IPF: A Tool to Assess Quality of Life in IPF; DLCO: diffusing capacity for carbon monoxide; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; HRCT, high resolution computed tomography; UIP, usual interstitial pneumonia.

[#] Values are median (range) unless otherwise noted. All values are from measurements at baseline visit (day of randomisation); eligibility was based on measurements at screening visit.

[¶] ATAQ-IPF total score range is 31–124.

TABLE 2. Summary of secondary endpoints

	Cohort A			Cohort B		
	Lebrikizumab (n=78)	**Placebo (n=76)**	***P* value**	**Lebrikizumab + pirfenidone (n=174)**	**Placebo + pirfenidone (n=177)**	***P* value**
Time-to-event analyses, HR (95% CI)						
PFS[#]	0.65 (0.39–1.09)		0.097[¶]	1.01 (0.72–1.42)		0.93[¶]
Time to first ≥10% absolute decline in % predicted FVC or all-cause mortality	0.79 (0.44–1.41)		0.42[¶]	0.84 (0.56–1.24)		0.37[¶]
Time to first ≥10% absolute decline in % predicted DLCO or all-cause mortality	0.72 (0.23–2.26)		0.56[¶]	0.68 (0.37–1.23)		0.19[¶]
Time to first respiratory hospitalisation	NA		NA	0.89 (0.52–1.54)		0.68[¶]
Time to first acute IPF exacerbation or death from any cause	1.21 (0.41–3.61)		0.73[¶]	0.61 (0.29–1.25)		0.17[¶]
Time to first SGRQ worsening ≥7 or all-cause mortality	0.84 (0.54–1.31)		0.44[¶]	NA		NA
Time to all-cause mortality through Week 52	1.01 (0.25–4.02)		0.99[¶]	0.42 (0.17–1.04)		0.053[¶]
Annualised rate of decrease in % predicted DLCO over 52 weeks						
Slope	−4.24	−4.78	0.607	−5.57	−5.75	0.780
Absolute difference	0.54			0.18		
Relative difference, %	11.3			3.2		
Decline ≥15% or death, n (%)	1 (2)	3 (6)		3 (2.5)	5 (4.5)	
Relative difference, %	−67.3			−44.9		
Annualised rate of decline in 6MWD						

Slope	−22.7	−44.6		−46.9	−25.6	
Absolute difference	21.9		0.312	−21.4		0.203
Relative difference, %	49.1			−83.7		
Annualised rate of decline in ATAQ-IPF total score over 52 weeks						
Slope	4.78	6.89		5.45	5.61	
Absolute difference	−2.10		0.385	−0.16		0.905
Relative difference, %	−30.5			−2.9		
Proportion of patients with ≥10% decline in % predicted FVC or death from any cause						
Decline ≥10% or death, n (%)	9 (16.4)	12 (22.6)	0.89	22 (16.4)	19 (15.8)	0.67
Relative difference, %	−27.7			3.7		

ATAQ-IPF: A Tool to Assess Quality of Life in IPF; DLCO: diffusing capacity for carbon monoxide; FVC: forced vital capacity; HR: hazard ratio; IPF: idiopathic pulmonary fibrosis; PFS: progression-free survival; SGRQ: St. George's Respiratory Questionnaire.

[#] PFS was defined as time from randomisation to the first occurrence of: death from any cause, non-elective hospitalization for any cause, relative decline in FVC (L) ≥10%.

[¶] Log rank.

TABLE 3. Overview of safety during the placebo-controlled period

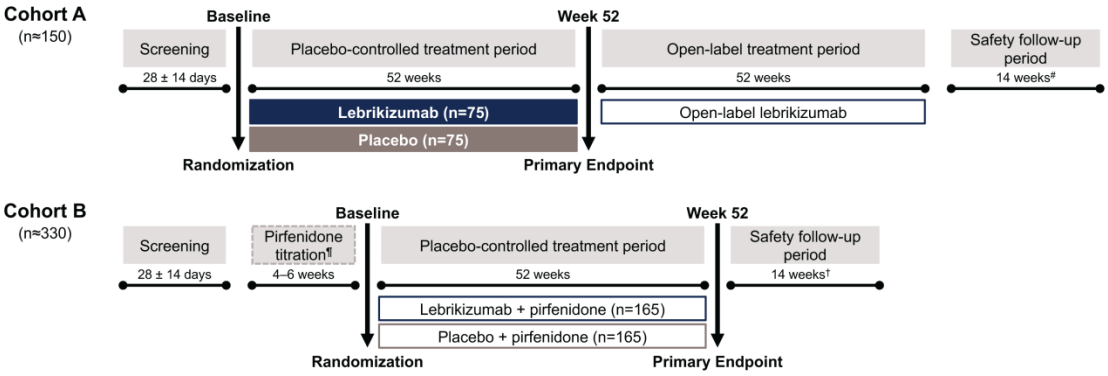
Event	Cohort A[¶]			Cohort B		
	Lebrikizumab (n=78)	**Placebo (n=76)**	**All patients (N=154)**	**Lebrikizumab + pirfenidone (n=174)**	**Placebo + pirfenidone (n=177)**	**All patients (N=351)**
Patients with ≥1 AE, n (%)	75 (96.2)	71 (93.4)	146 (94.8)	158 (90.8)	171 (96.6)	329 (93.7)
Total no. of AEs	531	446	977	1013	1052	2065
Deaths, n (%)	3 (3.8)	3 (3.9)	6 (3.9)	5 (2.9)	10 (5.6)	15 (4.3)
Patients withdrawn from study due to AE, n (%)	5 (6.4)	9 (11.8)	14 (9.1)	16 (9.2)	27 (15.3)	43 (12.3)
Patients with ≥1 AE with fatal outcome, n (%)	3 (3.8)	3 (3.9)	6 (3.9)	9 (5.2)	13 (7.3)	22 (6.3)
Patients with ≥1 SAE, n (%)	23 (29.5)	19 (25.0)	42 (27.3)	56 (32.2)	47 (26.6)	103 (29.3)
Patients with ≥1 SAE leading to withdrawal from treatment	6 (7.7)	6 (7.9)	12 (7.8)	12 (6.9)	14 (7.9)	26 (7.4)
Patients with ≥1 SAE leading to dose modification/interruption	5 (6.4)	3 (3.9)	8 (5.2)	6 (3.4)	4 (2.3)	10 (2.8)
Patients with ≥1 treatment-related SAE	2 (2.6)	1 (1.3)	3 (1.9)	3 (1.7)	6 (3.4)	9 (2.6)
Patients with ≥1 AE leading to withdrawal from treatment, n (%)	8 (10.3)	9 (11.8)	17 (11.0)	20 (11.5)	26 (14.7)	46 (13.1)
Patients with ≥1 AE leading to dose modification/interruption, n (%)	7 (9.0)	5 (6.6)	12 (7.8)	11 (6.3)	11 (6.2)	22 (6.3)
Patients with ≥1 treatment-related AE, n (%)	25 (32.1)	19 (25.0)	44 (28.6)	30 (17.2)	30 (16.9)	60 (17.1)
Patients with ≥1 treatment-related AE leading to withdrawal from treatment	0	2 (2.6)	2 (1.3)	3 (1.7)	8 (4.5)	11 (3.1)
Patients with ≥1 treatment-related AE leading to dose	2 (2.6)	0	2 (1.3)	1 (0.6)	1 (0.6)	2 (0.6)

modification/interruption						
AESIs, n (%)						
Injection-site reactions	13 (16.7)	6 (7.9)	19 (12.3)	5 (2.9)	5 (2.8)	10 (2.8)
Infections (broad)	51 (65.4)	41 (53.9)	92 (59.7)	106 (60.9)	114 (64.4)	220 (62.7)
Infections (narrow)	0	0	0	0	1 (0.6)	1 (0.3)
Malignancies[#]	5 (6.4)	2 (2.6)	7 (4.5)	13 (7.5)	12 (6.8)	25 (7.1)
AEs related to pirfenidone	5 (6.4)	3 (3.9)	8 (5.2)	64 (36.8)	70 (39.5)	134 (38.2)
AEs leading to withdrawal from pirfenidone	1 (1.3)	1 (1.3)	2 (1.3)	9 (5.2)	12 (6.8)	21 (6.0)

AE: adverse event; AESI: adverse event of special interest; NA: not available; SAE: serious adverse event.

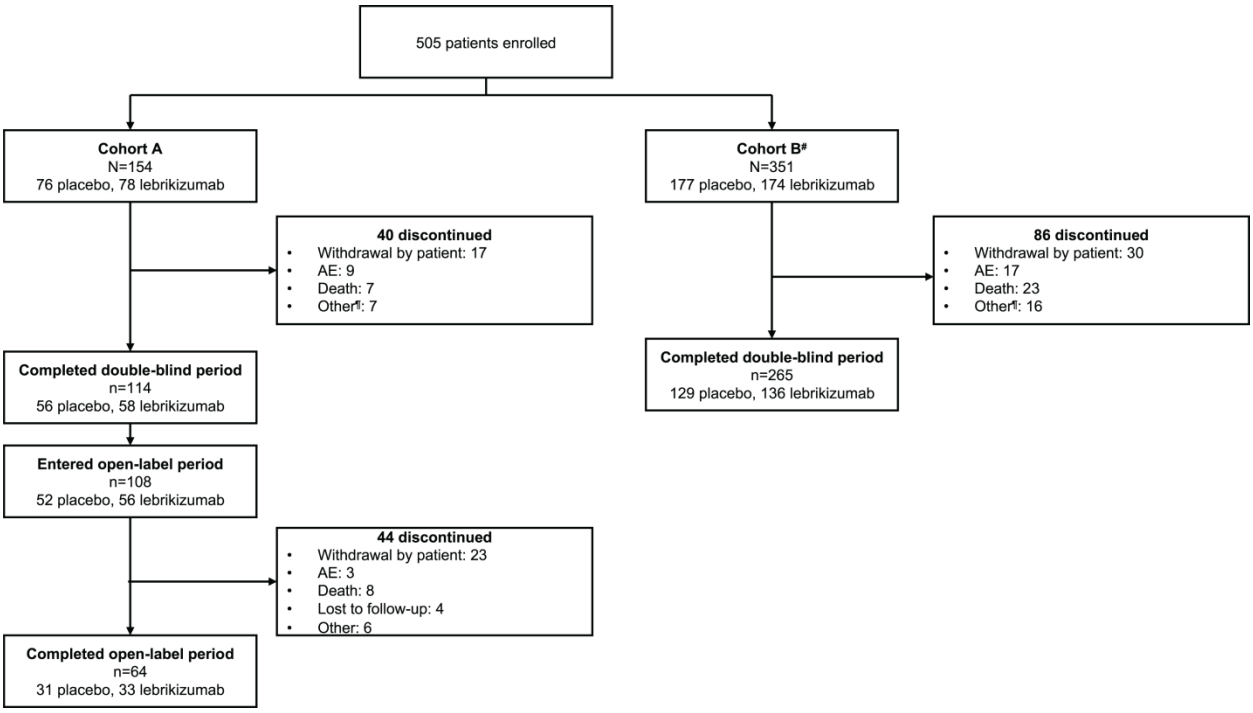
[#] Identified with Standardised Medical Dictionary for Regulatory Activities (MedDRA) Queries 'narrow.'

[¶] Patients were not required to stop study drug to be treated with pirfenidone

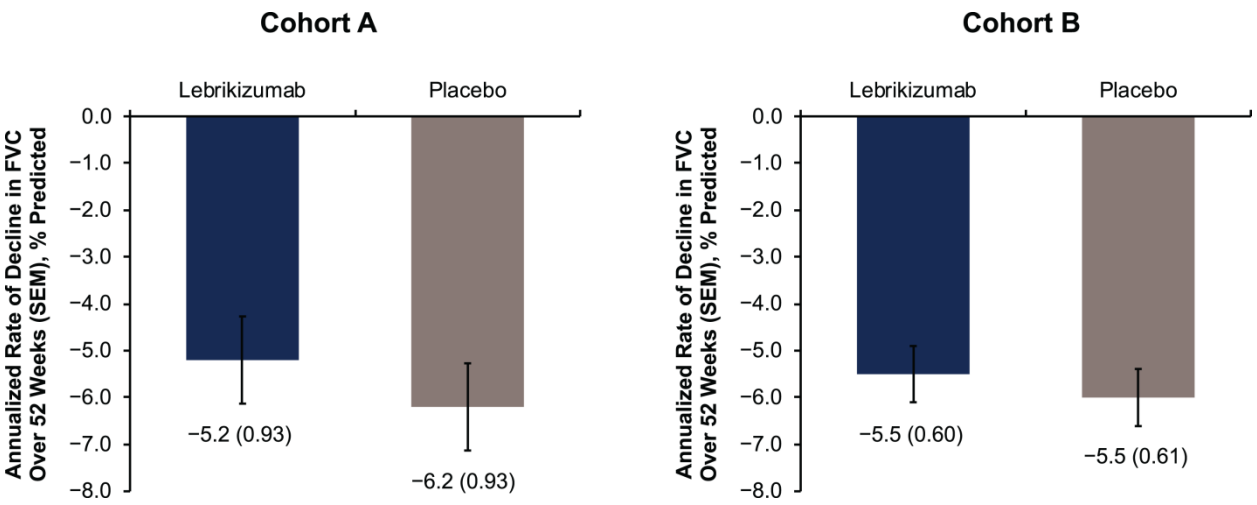


Study design

Safety follow-up ended 18 weeks after the last dose of study drug.¶ Titration period allowed for patients who were pirfenidone-naive at the time of enrolment.

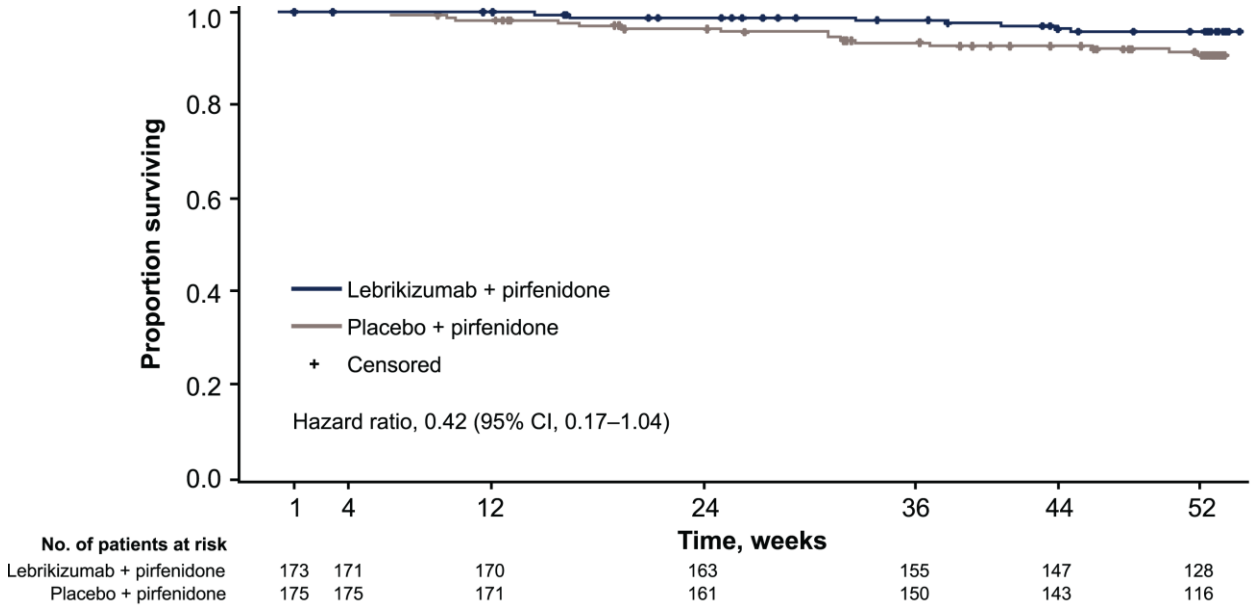


Patient disposition
AE: adverse event.
With background pirfenidone therapy.
¶ Other reasons for discontinuation during the placebo-controlled period included lack of efficacy, lost to follow-up, physician decision and protocol violation.



Annualised rate of decline in % predicted FVC over 52 weeks#
FVC: forced vital capacity.

Cohort B was receiving background pirfenidone therapy.



Time from randomisation to death from any cause in Cohort B

SUPPLEMENT:

Phase 2 trial to assess lebrikizumab in patients with idiopathic pulmonary fibrosis

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This supplement contains:

- Supplemental methods
- 3 supplemental figures
- 10 supplemental tables

Supplemental Methods

Ethics approvals

All participants provided informed, written consent. Approval of the study protocol was obtained from the institutional review board or independent ethics committee at each study site prior to study initiation. (See Supplemental table S9 for a full list of investigators and ethics approvals.)

Determination of sample size

The study was initially designed as a time-to-event trial to assess the benefit of lebrikizumab as monotherapy on progression-free survival (PFS). PFS was defined as time from randomisation to the first occurrence of: death from any cause, non-elective hospitalization for any cause, relative decline in FVC (L) ≥10%. After the approval of antifibrotic therapy to treat IPF in October 2014, the protocol was amended in January 2015 to add Cohort B to assess lebrikizumab vs. placebo with background pirfenidone. When the protocol was amended, the primary endpoint for both cohorts was changed from PFS to annualised rate of decline in % predicted forced vital capacity (FVC) through Week 52.

In Cohort A, it was estimated that a sample size of 75 patients in each treatment group would be needed to achieve ≈80% power to detect a 3.7% difference in the annualised rate of decline in % predicted FVC over 52 weeks. This is assuming a common SD of 8% (as reported in the placebo group of ASCEND) using a 2-group *t* test with a 0.05 two-sided significance level.

In Cohort B, it was estimated that a sample size of 165 patients in each treatment group would be needed to achieve ≈80% power to detect a 2.5% difference in the annualised rate of decline in % predicted FVC over 52 weeks. A similar assumption for the SD applied here.

Exclusion criteria

Key exclusion criteria included:

- History of severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity
- Evidence of other known causes of interstitial lung disease or clinically significant lung disease other than IPF
- Lung transplant expected within 12 months of screening
- Post-bronchodilator forced expiratory volume in 1 second (FEV_1)/FVC ratio <0.7
- Positive bronchodilator response indicated by an increase of ≥12% predicted and 200 mL increase in either FEV_1 or FVC
- Hospitalisation due to IPF exacerbation ≤4 weeks prior to or during screening
- Cardiac or liver disease, known current malignancy, infections or immunodeficiency
- Chronic oral corticosteroid therapy

Randomisation and blinding

Patients were randomised via an interactive voice/Web-based response system (IxRS). Within each cohort, dynamic hierarchical randomisation was performed centrally and stratified by the following:

- Region: United States, Europe/Canada, other
- Lung function: % predicted FVC <50%, 50% to 75%, <75%
- Serum periostin concentration: <50 ng/mL, ≥50 ng/mL

Patients, all study site personnel and the Sponsor were blinded to the treatment assignment throughout the placebo-controlled period. Treatment for each cohort was unblinded at the time of the primary analysis.

Dosing and administration

Lebrikizumab

All patients in Cohorts A and B received lebrikizumab 250 mg or placebo every 4 weeks for the 52-week placebo-controlled period. All patients received a total of 2 injections per dosing visit for a minimum of 13 doses of study treatment during the placebo-controlled, blinded, study treatment period. Patients in Cohort A who experienced confirmed disease progression, defined as ≥10% decline in FVC (mL/year, relative change) or non-elective hospitalisation, during the placebo-controlled period could initiate rescue therapy, including use of pirfenidone or nintedanib, at the investigator's discretion if approved by local regulatory authorities (see Supplemental table S10). During the open-label period, patients in Cohort A could add treatment with pirfenidone, nintedanib or other regionally approved IPF therapies at the investigator's discretion.

Pirfenidone

The recommended dose of pirfenidone is 2403 mg/day (or 1800 mg/day for patients in Japan) administered in divided doses 3 times per day (TID) with food. Patients in Cohort B who entered screening receiving stable pirfenidone were randomised to receive lebrikizumab or placebo. Patients in Cohort B who were treatment-naive to pirfenidone initiated titration during the run-in period over 14 days, as tolerated, to the full dose of 9 capsules per day (3 capsules TID) as follows:

- Days 1–7: 1 capsule TID
- Days 8–14: 2 capsules TID
- Day 15 and onward: 3 capsules TID

Combination treatment with pirfenidone and nintedanib was not permitted.

Biomarker assessments

CCL13 was measured using the R&D Systems Quantikine human CCL13-MCP-4 immunoassay (DCC130) with lower limit of quantification (LLOQ) of 31.2 pg/mL. CCL18 was measured using the IMPACTD R-CID10.01 chip with LLOQ of 6 ng/mL. Periostin was measured using the Elecys assay on a Cobas e601 instrument with LLOQ of 10 ng/mL.

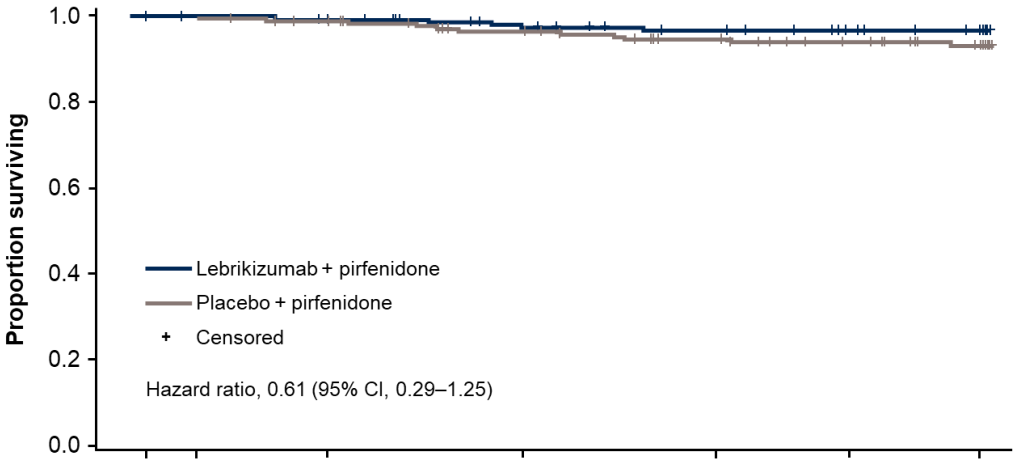
Immunogenicity

Lebrikizumab ADAs and PLBL2 antibodies were tested using a validated immunoassay by Covance Laboratories, Inc. (Chantilly, VA). The assay had a relative sensitivity 64 ng/mL of a surrogate positive control, a monoclonal anti-idiotypic antibody against lebrikizumab and 133 ng/mL of a surrogate positive control for monoclonal antibody against PLBL2. The assay could detect 500 ng/mL of this surrogate positive control in the presence of 50 µg/mL lebrikizumab or 250 ng/mL of this surrogate positive control in the presence of 200 ng/mL PLBL2.

A positive ADA sample was defined as one in which the presence of detectable ADAs could be confirmed by competitive binding with lebrikizumab. Treatment-induced ADA patients were those with negative or missing baseline ADA results and ≥1 positive post-baseline ADA result. Treatment-enhanced ADA patients were those with positive ADA results at baseline who then had ≥1 post-baseline titre result that were ≥0.6 more titre units than the baseline titre units. The baseline prevalence and post-baseline incidence of ADAs were calculated from the number of patients who tested ADA positive at baseline or post-baseline divided by either the total number of patients with evaluable samples at the baseline timepoint or post-baseline, respectively. Similar rules were used to define PLBL2 antibodies.

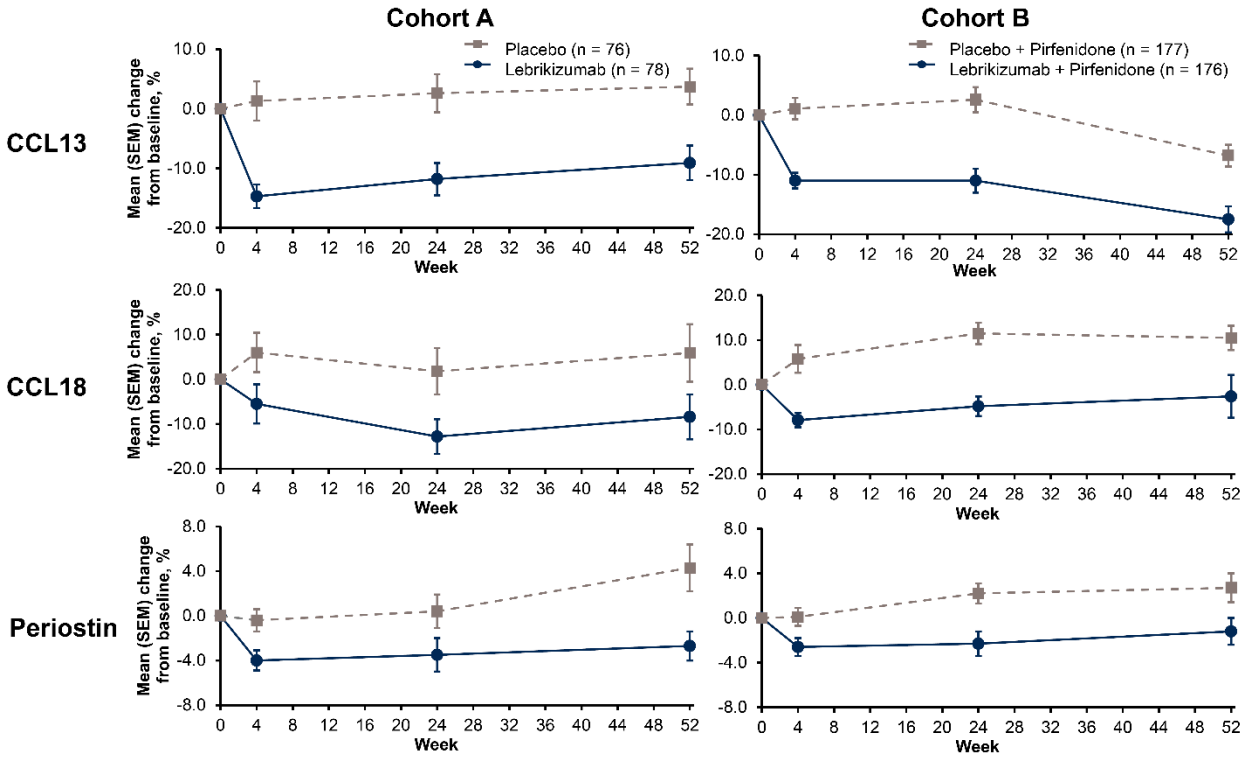
Supplemental Figures

SUPPLEMENTAL FIGURE S1. Time from randomisation to first acute exacerbation or death in Cohort B



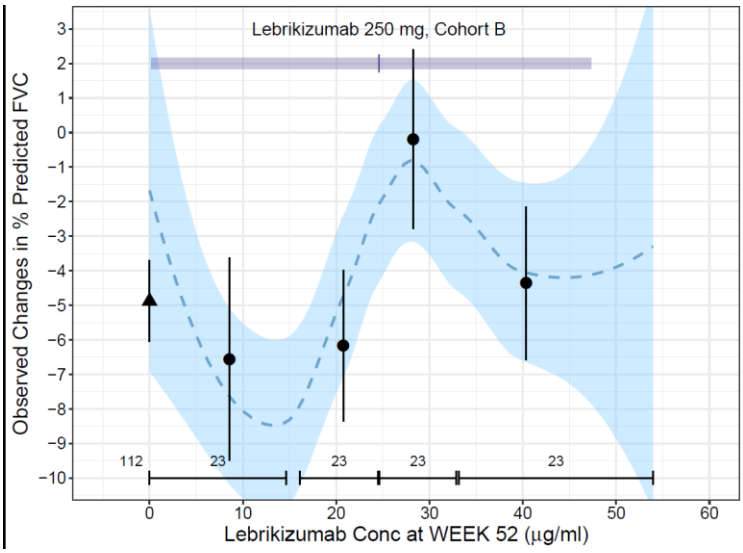
No. of patients at risk							
Lebrikizumab + pirfenidone	172	170	168	159	152	144	125
Placebo + pirfenidone	175	174	170	159	148	140	113
Cumulative no. of events by visit							
Lebrikizumab + pirfenidone	0	0	3	6	9	12	12 (6.9%)
Placebo + pirfenidone	0	2	7	12	16	17	19 (10.9%)

SUPPLEMENTAL FIGURE S2. Pharmacodynamics of biomarkers for lebrikizumab target engagement



CCL: chemokine C-C motif ligand.

SUPPLEMENTAL FIGURE S3. Relationship between lebrikizumab exposure and FVC change at Week 52



FVC: forced vital capacity.

Supplemental Tables

SUPPLEMENTAL TABLE S1. Baseline 6MWD data

Characteristic[#]	Cohort A			Cohort B		
	Lebrikizumab (n=78)	**Placebo (n=76)**	**All patients (N=154)**	**Lebrikizumab + pirfenidone (n=174)**	**Placebo + pirfenidone (n=177)**	**All patients (N=351)**
6MWD, m	436.5 (150.0–926.0)	455.5 (190.0–975.0)	450.0(150.0–975.0)	455 (156.0–996.3)	510 (118.0–9900)	480 (118.0–996.3)
Difference in Borg scale[+]	1.5 (−2.0–9.5)	2.0 (−1.0–10.0)	2.0 (−2.0–10.0)	2.0 (−2.7–9.5)	2.0 (−2.5–9.5)	2.0 (−2.7–9.5)

6MWD, 6-minute walk distance.

[#] Values are median (range) unless otherwise noted. All values are from measurements at baseline visit (day of randomisation); eligibility was based on measurements at screening visit.

[¶] Results may not be reliable due to inconsistency with reporting and measurement between study sites.

[+] Baseline difference in Borg scale represents change in dyspnoea after the 6MWD test compared with before the test. The Borg scale range is 0–10.

SUPPLEMENTAL TABLE S2. Concomitant medications reported during the placebo-controlled period

Patients reporting concomitant medication use, n (%)[#]	Cohort A			Cohort B		
	Lebrikizumab (n=78)	Placebo (n=76)	All patients (n=154)	Lebrikizumab + pirfenidone (n=174)	Placebo + pirfenidone (n=177)	All patients (n=351)
≥ 1 concomitant medication	77 (98.7)	76 (100.0)	153 (99.4)	174 (100.0)	174 (98.3)	348 (99.1)
Medication use by class[¶]						
Proton pump inhibitors	52 (66.7)	44 (57.9)	96 (62.3)	125 (71.8)	122 (68.9)	247 (70.4)
Statins	41 (52.6)	35 (46.1)	76 (49.4)	86 (49.4)	85 (48.0)	171 (48.7)
Steroids	27 (34.6)	28 (36.8)	55 (35.7)	93 (53.4)	98 (55.4)	191 (54.4)
Salicylates	36 (46.2)	34 (44.7)	70 (45.5)	78 (44.8)	88 (49.7)	166 (47.3)
Antihistamines	21 (26.9)	20 (26.3)	41 (26.6)	59 (33.9)	73 (41.2)	132 (37.6)
Analgesics	26 (33.3)	28 (36.8)	54 (35.1)	50 (28.7)	66 (37.3)	116 (33.0)
Herbal, homeopathic and dietary supplements	32 (41.0)	24 (31.6)	56 (36.4)	51 (29.3)	60 (33.9)	111 (31.6)
Non-steroidal anti-inflammatory drugs	26 (33.3)	30 (39.5)	56 (36.4)	52 (29.9)	54 (30.5)	106 (30.2)
Cough preparations	23 (29.5)	15 (19.7)	38 (24.7)	48 (27.6)	63 (35.6)	111 (31.6)
Vaccines, toxoids and serologic agents	25 (32.1)	25 (32.9)	50 (32.5)	41 (23.6)	52 (29.4)	93 (26.5)
Macrolide antibiotics	17 (21.8)	15 (19.7)	32 (20.8)	50 (28.7)	46 (26.0)	96 (27.4)
β-adrenoceptor blocking agents	23 (29.5)	15 (19.7)	38 (24.7)	43 (24.7)	47 (26.6)	90 (25.6)
Bronchodilators and anti-asthmatic drugs	13 (16.7)	15 (19.7)	28 (18.2)	38 (21.8)	56 (31.6)	94 (26.8)
Angiotensin II receptor antagonists	22 (28.2)	19 (25.0)	41 (26.6)	37 (21.3)	38 (21.5)	75 (21.4)
Penicillins	17 (21.8)	10 (13.2)	27 (17.5)	27 (15.5)	54 (30.5)	81 (23.1)
Quinolone antibiotics	17 (21.8)	14 (18.4)	31 (20.1)	37 (21.3)	32 (18.1)	69 (19.7)

[#] Concomitant medication use occurred at any time from first dose of study treatment through the end of the placebo-controlled period.

[¶] Concomitant medication classes reported in ≥ 20% of patients in either Cohort A or Cohort B are shown. When pirfenidone was excluded as a concomitant medication, < 1% and 2% of patients in Cohort A and Cohort B, respectively, received immunosuppressants. Medications were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.1.

SUPPLEMENTAL TABLE S3. Baseline biomarker levels

Biomarker[#]	Cohort A			Cohort B		
	Lebrikizumab (n=78)	**Placebo (n=76)**	**All patients (N=154)**	**Lebrikizumab + pirfenidone (n=174)**	**Placebo + pirfenidone (n=177)**	**All patients (N=351)**
CCL13, pg/mL	264.0 (215.2–324.7)	270.9 (222.4–339.4)	270.5 (219.8–333.9)	302.0 (225.6, 381.7)	295.2 (244.2–383.7)	296.9 (229.3–382.1)
CCL18, ng/mL	628.6 (399.7–873.8)	659.9 (341.5–900.6)	657.5 (360.5–882.3)	269.8 (205.0–357.7)	275.0 (217.5–374.6)	273.5 (211.3–363.2)
Periostin, ng/mL	64.4 (54.7–81.0)	66.9 (57.2–80.7)	65.6 (56.1–80.9)	62.2 (54.9–74.1)	64.8 (53.0–79.0)	63.5 (53.4–75.4)

CCL: chemokine C-C motif ligand.

[#] Values are median (interquartile range).

SUPPLEMENTAL TABLE S4. Summary of pharmacokinetics following lebrikizumab administration

Cohort	Treatment	Summary	Mean (SD)					
			Week 4 $C_{min,}$ µg/mL	Week 12 $C_{min,}$ µg/mL	Week 24 $C_{min,}$ µg/mL	Week 36 $C_{min,}$ µg/mL	Week 52 $C_{min,}$ µg/mL	$t_{1/2}$, days
A	Lebrikizumab 250 mg	N	74	68	65	2	61	35
		Mean (SD)	14.0 (4.86)	24.4 (9.86)	28.5 (12.5)	29.6 (14.1)	28.5 (14.0)	23.5 (5.36)
B	Lebrikizumab 250 mg + pirfenidone	N	170	165	153	146	137	125
		Mean (SD)	14.9 (5.75	25.1 (11.0)	25.7 (12.4)	25.6(13.8)	25.2(12.7	21.9 (4.79)

C_{min}: observed minimum serum concentration; $t_{1/2}$: elimination half-life.

SUPPLEMENTAL TABLE S5. Treatment exposure

	Cohort A			Cohort B		
	Lebrikizumab (n=78)	**Placebo (n=76)**	**All patients (N=154)**	**Lebrikizumab + pirfenidone (n=174)**	**Placebo + pirfenidone (n=177)**	**All patients (N=351)**
Lebrikizumab or placebo exposure during the placebo-controlled period						
Treatment duration, mean (SD), weeks	44.7 (18.3)	44.9 (18.0)	44.8 (18.1)	42.4 (13.1)	41.3 (13.1)	41.8 (13.1)
No. of doses, mean (SD)	12.0 (4.5)	12.1 (4.4)	12.0 (4.5)	11.4 (3.3)	11.2 (3.3)	11.3 (3.3)
Lebrikizumab exposure period[#]						
	Lebrikizumab to lebrikizumab (n=78)	**Placebo to lebrikizumab (n=52)**	**All patients (N=130)**			
Treatment duration, mean (SD), weeks	79.1 (38.6)	39.3(15.0)	63.2 (36.9)	–	–	–
No. of doses, mean (SD)	20.5 (9.6)	10.8 (3.8)	16.6 (9.1)	–	–	–
Pirfenidone exposure during the placebo-controlled period						
Treatment duration, mean (SD), weeks	–	–	–	46.7 (12.7)	44.9 (13.4)	45.8 (13.1)
Daily dose, mean (SD), mg	–	–	–	2088.6 (470.6)	2053.4 (504.2)	2070.9 (487.5)

[#] The lebrikizumab exposure period included all adverse events reported from the first dose of study drug until the end of safety follow-up. This included patients who were randomised to receive lebrikizumab and all patients who received lebrikizumab during the open-label treatment period (including patients who were randomised to receive placebo).

SUPPLEMENTAL TABLE S6. Summary of AEs by preferred terms in ≥10% of patients in any treatment arm during the placebo-controlled period

AE	Cohort A		Cohort B	
	Lebrikizumab (n=78)	**Placebo (n=76)**	**Lebrikizumab + pirfenidone (n=174)**	**Placebo + pirfenidone (n=177)**
Cough	17 (21.8)	13 (17.1)	28 (16.1)	43 (24.3)
IPF	15 (19.2)	16 (21.1)	24 (13.8)	29 (16.4)
Dyspnoea	12 (15.4)	8 (10.5)	13 (7.5)	17 (9.6)
Fatigue	11 (14.1)	8 (10.5)	26 (14.9)	19 (10.7)
Nasopharyngitis	11 (14.1)	15 (19.7)	29 (16.7)	24 (13.6)
Upper respiratory tract infection	11 (14.1)	10 (13.2)	29 (16.7)	36 (20.3)
Bronchitis	10 (12.8)	7 (9.2)	17 (9.8)	11 (6.2)
Diarrhoea	8 (10.3)	10 (13.2)	17 (9.8)	19 (10.7)
Dizziness	8 (10.3)	9 (11.8)	7 (4.0)	11 (6.2)
Headache	7 (9.0)	9 (11.8)	10 (5.7)	15 (8.5)
Arthralgia	5 (6.4)	8 (10.5)	10 (5.7)	7 (4.0)
Nausea	7 (9.0)	4 (5.3)	22 (12.6)	18 (10.2)
Vascular disorders	4 (5.1)	7 (9.2)	19 (10.9)	13 (7.3)
Photosensitivity reaction	2 (2.6)	1 (1.3)	6 (3.4)	22 (12.4)
Rash	6 (7.7)	4 (5.3)	16 (9.2)	20 (11.3)
Decreased appetite	3 (3.8)	3 (3.9)	15 (8.6)	18 (10.2)

AE: adverse event; IPF: idiopathic pulmonary fibrosis.

SUPPLEMENTAL TABLE S7. Summary of AEs by preferred terms in ≥10% of patients in either arm of Cohort A during the lebrikizumab exposure period[#]

AE	Lebrikizumab (N=130)
Any	126 (96.9)
IPF	31 (23.8)
Cough	28 (21.5)
Nasopharyngitis	27 (20.8)
Diarrhoea	24 (18.5)
Bronchitis	22 (16.9)
Upper respiratory tract infection	21 (16.2)
Dyspnoea	20 (15.4)
Fatigue	19 (14.6)
Constipation	17 (13.1)
Dizziness	17 (13.1)
Back pain	15 (11.5)
Nausea	15 (11.5)
Urinary tract infection	15 (11.5)
Lower respiratory tract infection	14 (10.8)

AE: adverse event; IPF: idiopathic pulmonary fibrosis.

[#] The lebrikizumab exposure period included all adverse events reported from the first dose of study drug until the end of safety follow-up. This included patients who were randomised to receive lebrikizumab and all patients who received lebrikizumab during the open-label treatment period (including patients who were randomised to receive placebo).

SUPPLEMENTAL TABLE S8. Summary of causes of death

Deaths, n (%)	Cohort A			Cohort B		
	Lebrikizumab	**Placebo**	**All patients**	**Lebrikizumab + pirfenidone**	**Placebo + pirfenidone**	**All patients**
Total, at any time	15	4	19	11	18	29
Placebo-controlled period	**(n=78)**	**(n=76)**	**(N=154)**	**(n=174)**	**(n=177)**	**(N=351)**
All causes[#]	3 (3.8)	3 (3.9)	6 (3.9)	9 (5.2)	13 (7.3)	22 (6.3)
IPF	2	1	3	5	8[¶]	13
Pneumonia	0	0	0	1	1	2
Pulmonary embolism	1[¶]	0	1	0	0	0
Acute respiratory failure	0	1	1	0	1	1
Sudden death	0	1	1	0	0	0
Graft vs. host disease	0	0	0	1	0	1
Septic shock	0	0	0	1	0	1
Cardiovascular accident	0	0	0	1	0	1
Dyspnoea	0	0	0	0	1	1
Pulmonary fibrosis	0	0	0	0	1	1
Respiratory failure	0	0	0	0	1	1
Lebrikizumab exposure period[+]	**(N=130)**					
All causes, at any time	15 (11.5)	–	–	–	–	–
During placebo-controlled period (above)	3[§]	–	–	–	–	–
During open-label lebrikizumab	9	–	9	–	–	–
IPF	4	–	4	–	–	–
IPF and hypoxia	1	–	1	–	–	–
Acute myocardial infarction	1	–	1	–	–	–

Malignant lung neoplasm	1	–	1	–	–	–
Lower respiratory tract infection	1	–	1	–	–	–
Acute respiratory failure	1[¶]	–	1[¶]	–	–	–
During safety follow-up (below)	3[§]	–	–	–	–	–
Safety follow-up						
All causes	3[f]	1	4	2	5	7
IPF	2	1[¶]	3	0	4	4
Pleural effusion	1	0	1	0	1	1
Cardiac failure	0	0	0	2	0	2

[#] Including deaths that occurred ≤30 days after last dose of lebrikizumab; this count does not match the count of deaths for the efficacy analysis, which excluded deaths after lung transplant or after the 52-week placebo-controlled period.

[¶] Included 1 death that was assessed by the investigator to be treatment related.

[+] The lebrikizumab exposure period included all AEs reported from the first dose of study drug until the end of safety follow-up. This included patients who were randomised to receive lebrikizumab and all patients who received lebrikizumab during the open-label treatment period (including patients who were randomised to receive placebo).

[§] Of 15 deaths that occurred during the lebrikizumab exposure period, 3 were also counted during the placebo-controlled period (lebrikizumab arm) and 3 were also counted during safety follow-up.

[f] Included 2 patients in safety follow-up after double-blind lebrikizumab treatment and 1 after open-label lebrikizumab treatment after having received placebo.

SUPPLEMENTAL TABLE S9. List of investigators and ethics review approvals for each study site by country

Country	Investigator	Institutional review board/independent ethics committee name and address (if available)	Approval date
Australia	A. Glanville	SSWAHS Ethics Review Committee (RPAH Zone), c/- Research Development Office Level 3, Building 92, Missenden Road, 2050, Camperdown, NSW, Australia	08 Sep 2015
Australia	I. Glaspole	The Alfred Hospital Research Ethics Committee, The Alfred Hospital, 55 Commercial Road, 3004, Melbourne, VIC, Australia	17 Feb 2014
Australia	M. Phillips	Bellberry Human Research Ethics Committee, Bellberry Limited, 229 Greenhill Road, 5065, Dulwich, SA, Australia	16 Oct 2013
Australia	F. Thien	Northern Sydney Local Health District Human Research Ethics Committee, Level 13, Kolling Building, 2065, St. Leonards, NSW, Australia	28 Mar 2014
Australia	L. Troy	SSWAHS Ethics Review Committee (RPAH Zone), c/- Research Development Office Level 3, Building 92, Missenden Road, 2050, Camperdown, NSW, Australia	10 Apr 2014
Belgium	B. Bondue	Central EC, Commissie Medische Ethiek UZ KU Leuven, Campus Gasthuisberg E330 Herestraat 49, 3000 Leuven	28 Apr 2014
Belgium	C. Dahlqvist	Central EC, Commissie Medische Ethiek UZ KU Leuven, Campus Gasthuisberg E330 Herestraat 49, 3000 Leuven	28 Apr 2014
Belgium	T. Pieters	Central EC, Commissie Medische Ethiek UZ KU Leuven, Campus Gasthuisberg E330 Herestraat 49, 3000 Leuven	28 Apr 2014
Belgium	W. Wuyts	Central EC, Commissie Medische Ethiek UZ KU Leuven, Campus Gasthuisberg E330 Herestraat 49, 3000 Leuven	28 Apr 2014
Canada	N. Khalil	University of British Columbia Office of Research Services, 102-6190 Agronomy Road, Vancouver, BC Canada V6T 1Z3	25 Nov 2013
Canada	M. Mura	Western University Research Support Services Bldg., Rm. 5150, London, ON, Canada N6G 1G9	1 Nov 2013
Canada	S. Provencher	Institut Universitaire de Cardiologie et de Pneumologie de Quebec 2725 chemin Sainte-Foy, Local 2614, QC, Canada G1V 4G5	28 Jan 2014
France	B. Crestani	CPP Ile de France I, Hotel Dieu, 1 Place du Parvis de Notre-Dame, 75181, Paris, France	17 Sep 2013
France	S. Jouneau	CPP Ile de France I, Hotel Dieu, 1 Place du Parvis de Notre-Dame, 75181, Paris, France	17 Sep 2013
France	H. Nunes	CPP Ile de France I, Hotel Dieu, 1 Place du Parvis de Notre-Dame, 75181, Paris, France	17 Sep 2013
France	B. Wallaert	CPP Ile de France I, Hotel Dieu, 1 Place du Parvis de Notre-Dame, 75181, Paris, France	17 Sep 2013
Germany	J. Behr	EK Essen Ethik-Kommission der Medizinischen Fakultät der Universität Duisburg-Essen, Robert-Koch-Str. 9-11, 45147 Essen, Germany	4 Nov 2013
Germany	U. Costabel	EK Essen Ethik-Kommission der Medizinischen Fakultät der Universität Duisburg-Essen, Robert-Koch-Str. 9-11, 45147 Essen, Germany	4 Nov 2013
Germany	A. Günther	EK Essen Ethik-Kommission der Medizinischen Fakultät der Universität Duisburg-Essen, Robert-Koch-Str. 9-11, 45147 Essen, Germany	4 Nov 2013
Germany	P. Hammerl	EK Essen Ethik-Kommission der Medizinischen Fakultät der Universität Duisburg-Essen, Robert-Koch-Str. 9-11, 45147 Essen, Germany	4 Nov 2013
Germany	A.-M. Kirsten	EK Essen Ethik-Kommission der Medizinischen Fakultät der Universität Duisburg-Essen, Robert-Koch-Str. 9-11, 45147 Essen, Germany	4 Nov 2013
Germany	M. Kreuter	EK Essen Ethik-Kommission der Medizinischen Fakultät der Universität Duisburg-Essen, Robert-Koch-Str. 9-11, 45147 Essen, Germany	4 Nov 2013
Italy	S. Harari	IRCCS Multimedica Sezione Comitato Etico Centrale IRCCS Regione Lombardia, Via Milanese 300, 20099 Sesto San Giovanni (MI) Italy	18 Feb 2014
Italy	P. Rottoli	Comitato Etico Area Vasta Sud, Est, viale Bracci 16, 53100, Siena, Toscana, Italy	19 Nov 2013
Italy	S. Tomassetti	Comitato Etico Di Area Vasta Romagna E Irst, Via Piero Maroncelli, 40, 47014 Meldola (FC), Italy	16 Apr 2014
Italy	C. Vancheri	Comitato Etico Catania 1, Azienda Ospedaliero, Universitaria “Policlinico - Vittorio Emanuele,” via S.Sofia, 78, 95123 Catania, Italy	10 Dec 2013

Country	Investigator	Institutional review board/independent ethics committee name and address (if available)	Approval date
Japan	Y. Inoue	Institutional Review Board of National Hospital Organization Kinki - Chuo Chest Medical Center, 1180, Nagasonecho, Kita-ku, Sakai-shi Osaka, Japan 591-8555	12 Dec 2014
Japan	Y. Kondoh	Tosei General Hospital IRB 160, Nishioiwakecho, Seto-shi, Aichi, Japan 489-8642	26 Nov 2014
Japan	T. Ogura	Kanagawa Cardiovascular and, Respiratory Center Institutional Review, Board, 6-16-1, Tomioka-higashi, Kanazawa-ku, Kanagawa, Yokohama, Japan 236-0051	10 Dec 2014
Mexico	U. Chavarria Martinez	Comité de Ética en Investigación de la Facultad de Medicina y Hospital Universitario de la UANL, Av. Francisco I Madero y Av. Gonzalitos S/N, Col. Mitras, Centro Monterrey Nuevo Leon, 64460, Monterrey Nuevo Leon, Mexico	20 Dec 2013
Mexico	A. Ramirez	CEI Unidad de Investigacion Clinica en Medicina S.C; Comite de Etica en Investigacion, Av. La clinica No. 2520 - 522 y 524, Col. Sertoma, 64718, Monterrey, Nuevo Leon, Mexico	8 Oct 2013
Mexico	M. Selman Lama	CEI INER Ismael Cosio; Comite de Etica en Investigacion, Instituto Nacional de Enfermedades Respiratorias, Calz. de Tlalpan 4502 Del. Tlalpan, Col. Seccion XVI, Ciudad de México. C.P. 14080, Mexico	19 Feb 2014
Peru	S. Castro	Asociación Benefica Prisma EC, Av. Carlos Gonzales 251, Maranga, L-32, Lima, Peru	15 Nov 2013
Peru	A. G. Guerreros Benavides	Asociación Benefica Prisma EC, Carlos Gonzales 251, San Miguel 15088, Lima, Peru	22 Jan 2015
Peru	A. Matsuno	Asociación Benefica Prisma EC, Av. Carlos Gonzales 251, Maranga, L-32, Lima, Peru	23 Oct 2013
Poland	H. Batura-Gabryel	Komisja Bioetyki Uniwersytetu Medycznego w Lodzi, Al. Kosciuszki 4, 90-, 419, Lodz, Poland	11 Feb 2014
Poland	J. Kus	Komisja Bioetyki Uniwersytetu Medycznego w Lodzi, Al. Kosciuszki 4, 90-, 419, Lodz, Poland	11 Mar 2014
Poland	W. Piotrowski	Komisja Bioetyki Uniwersytetu Medycznego w Lodzi, Al. Kosciuszki 4, 90-, 419, Lodz, Poland	24 Sep 2013
Spain	J. Ancochea Bermudez	Hospital Universitario la Princesa; Comité, Etico de Investigacion Clinica, C/ Diego de Leon, 62, 28006, Madrid, Spain	16 Sep 2013
Spain	E. Fernandez-Fabrellas	CEIC Hospital General Universitario de Valencia, Avda. Tres Cruces s/n, 46014, Valencia, Spain	16 Sep 2013
Spain	M. Molina Molina	CEIC Hospital de Bellvitge, Carrer de la Feixa Llarga, s/n, 08907 L'Hospitalet de Llobregat, Barcelona, Spain	20 Sep 2013
Spain	A. Nieto Barbero	CEIC Hospital Clinico San Carlos, Farmacologia/1 planta Norte. Puerta G., Professor Martin Lagos s/n, 28040, Madrid, Spain	12 Feb 2014
Spain	J. A. Rodriguez-Portal	CEIC Hospital de Bellvitge, Carrer de la Feixa Llarga, s/n, 08907 L'Hospitalet de Llobregat, Barcelona, Spain	16 Dec, 2013
United Kingdom	H. Adamali	Southmead Hospital; Respiratory Department; Research & Innovation, Southmead Road, Westbury-on-Trym, Bristol, BS10 5NB, UK	31 Jan 2014
United Kingdom	P. Beirne	London - Hampstead Research Ethics Committee, Barlow House 3rd Floor, 4 Minshull Street Manchester, M1 3DZ, UK	31 Jan 2014
United Kingdom	Z. Borrill	London - Hampstead Research Ethics Committee, Barlow House 3rd Floor, 4 Minshull Street Manchester, M1 3DZ, UK	6 Nov 2013
United Kingdom	S. Fletcher	Southampton General Hospital; R&D (Trust), R&D office, Mailpoint 138, Duthie building (trust), Tremona Road, Southampton, SO16 6YD, UK	6 Nov 2013
United Kingdom	T. Maher	London - Hampstead Research Ethics Committee, Barlow House 3rd Floor, 4 Minshull Street Manchester, M1 3DZ, UK	6 Nov 2013
United Kingdom	H. Parfrey	Papworth Hospital NHS Foundation Trust; Respiratory Department; Research and Development office, Papworth Everard, Cambridge, CB23 3RE, UK	21 Mar 2014
United Kingdom	L. Spencer	London - Hampstead Research Ethics Committee, Barlow House 3rd Floor, 4 Minshull Street Manchester, M1 3DZ, UK	6 Nov 2013
United States	D. Antin-Ozerkis	Yale University IRB, 150 Munson St., 3rd Floor, P.O. Box 208327, New Haven CT, 06520-8327, USA	18 Oct 2013

Country	Investigator	Institutional review board/independent ethics committee name and address (if available)	Approval date
United States	A. Awab	University of Oklahoma IRB, 1000 Stanton L. Young Blvd, LIB176, Oklahoma City, OK 73117, USA	26 Jan 2014
United States	R. Bascom	Hershey Medical Center; Institutional Review Board, 600 Centerview Drive, Mail Code A115, Rm 1140, Hershey, PA, 17033, USA	17 Dec 2013
United States	N. Bhatt	Western International Review Board, 3535 Seventh Avenue SW, P.O. Box 12029, Olympia, WA, 98502-5010, USA	4 Nov 2013
United States	E. J. Britt	University of Maryland, Baltimore IRB 620 W Lexington St., Baltimore, MD 21201, USA	24 Sep 2013
United States	A. H. Case	Piedmont Healthcare, 1968 Peachtree Road, NW Atlanta, Georgia 30309, USA	11 Nov 2013
United States	C. Daniels	Mayo Clinic IRB, 201 Building, Room 4-60, 200 First St. SW, Rochester, MN 55905, USA	14 Mar 2014
United States	J. A. De Andrade	Western International Review Board, 3535 Seventh Avenue SW, P.O. Box 12029, Olympia, WA, 98502-5010, USA	1 Oct 2013
United States	K. DeBoer	Western International Review Board, 3535 Seventh Avenue SW, P.O. Box 12029, Olympia, WA, 98502-5010, USA	17 Jul 2013
United States	T. DeMarini	Western International Review Board, 3535 Seventh Avenue SW, P.O. Box 12029, Olympia, WA, 98502-5010, USA	22 Jul 2014
United States	D. Dilling	Loyola University Chicago Health Sciences Division IRB, 2160, S First Ave., Maywood, IL, 60153, USA	2 Oct 2013
United States	J. Dorf	Western International Review Board, 3535 Seventh Avenue SW, P.O. Box 12029, Olympia, WA, 98502-5010, USA	23 Apr 2014
United States	N. Ettinger	St. Luke's Hospital IRB Office 2732, 4401 Wornall Road, Kansas City, MO 64111, USA	4 Sep 2013
United States	J. Ferguson	Western International Review Board, 3535 Seventh Avenue SW, P.O. Box 12029, Olympia, WA, 98502-5010, USA	30 Jul 2013
United States	A. K. Gerke	Western International Review Board, 3535 Seventh Avenue SW, P.O. Box 12029, Olympia, WA, 98502-5010, USA	10 Jan 2014
United States	K. Gibson	WIRB, 1019 39th Avenue SE, Suite 120, Puyallup, WA, 98374-2115, USA	24 Oct 2013
United States	M. Glassberg	University of Miami Human Subjects Research Office (M809), P.O. Box 016980, 1500 NW 12 Avenue, Suite 1002, Miami, Florida 33136, USA	5 Nov 2013
United States	J. A. Golden	University of California, San Francisco IRB Human Research Protection Program, Box 09623333 California Street, Suite 315, San Francisco, CA 94143, USA	7 Jun 2015
United States	N. Gupta	Western International Review Board, 3535 Seventh Avenue SW, P.O. Box 12029, Olympia, WA, 98502-5010, USA	1 Oct 2013
United States	T. Haddad	Western International Review Board, 3535 Seventh Avenue SW, P.O. Box 12029, Olympia, WA, 98502-5010, USA	6 Jun 2014
United States	M. Hamblin	University of Kansas Medical Center/Human Subjects Committee, MS-1032, 3901 Rainbow Blvd., Kansas City, KS, 66160, USA	17 Dec 2013
United States	C. Himanshu	Western International Review Board, 3535 Seventh Avenue SW, P.O. Box 12029, Olympia, WA, 98502-5010, USA	26 Mar 2014
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United States	B. Shea	Lifespan, Research Protection Office, CORO West, Suite 1.300, One Hoppin Street, Providence, RI 02903, USA	26 Jul 2013
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United States	W. Strauss	Western International Review Board, 3535 Seventh Avenue, SW, P.O. Box 12029, Olympia, WA, 98502-5010, USA	18 Jul 2013
United States	J. Swigris	Western International Review Board, 3535 Seventh Avenue, SW, P.O. Box 12029, Olympia, WA, 98502-5010, USA	1 Aug 2013
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United States	M. L. Wencel	Via Christi Hospitals Wichita, Inc. IRB, 1100 N St. Francis, Suite 300, Wichita, KS 67214, USA	12 Jul 2013

SUPPLEMENTAL TABLE S10. Patients receiving antifibrotics as rescue therapy in Cohort A during the placebo-controlled period

Patients Receiving Antifibrotic Therapy, n (%)	Cohort A		
	Lebrikizumab (n=78)	Placebo (n=76)	All patients (N=154)
Pirfenidone	13 (16.7)	8 (10.5)	21 (13.6)
Nintedanib	1 (1.3)	3 (3.9)	4 (2.6)