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The natural history of progressive fibrosing interstitial lung diseases

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Abstract

We used data from the INBUILD and INPULSIS trials to investigate the natural history of progressive fibrosing interstitial lung diseases (ILDs).

Subjects in the two INPULSIS trials had a clinical diagnosis of idiopathic pulmonary fibrosis (IPF) while subjects in the INBUILD trial had a progressive fibrosing ILD other than IPF and met protocol-defined criteria for ILD progression despite management. Using data from the placebo groups, we compared the rate of decline in forced vital capacity (FVC) (mL/year) and mortality over 52 weeks in the INBUILD trial with pooled data from the INPULSIS trials.

The adjusted mean annual rate of decline in FVC in the INBUILD trial (n=331) was similar to that observed in the INPULSIS trials (n=423) (−192.9 and −221.0 mL/year, respectively; nominal p-value: 0.19). The proportion of subjects who had a relative decline in FVC >10% predicted at week 52 was 48.9% in the INBUILD trial and 48.7% in the INPULSIS trials, and the proportion who died over 52 weeks was 5.1% in the INBUILD trial and 7.8% in the INPULSIS trials. A relative decline in FVC >10% predicted was associated with an increased risk of death in the INBUILD (hazard ratio 3.64) and INPULSIS (hazard ratio 3.95) trials.

These findings indicate that patients with fibrosing ILDs other than IPF, who are progressing despite management, have a subsequent clinical course similar to patients with untreated IPF, with a high risk of further ILD progression and early mortality.

Introduction

Idiopathic pulmonary fibrosis (IPF) is, by definition, a progressive fibrosing interstitial lung disease (ILD) [1]. In addition to IPF, there are a number of other ILDs that may develop a progressive fibrosing phenotype characterised by declining lung function, an increasing extent of fibrosis on high resolution computed tomography (HRCT), worsening symptoms and quality of life, and early mortality [2-5]. Along with these clinical similarities, progressive fibrosing ILDs appear to share pathobiological mechanisms that may represent a common fibrotic response to tissue injury [6-10].

The ILDs that can be complicated by progressive fibrosis include idiopathic non-specific interstitial pneumonia (iNSIP) [11], unclassifiable idiopathic interstitial pneumonia (IIP) [12], hypersensitivity pneumonitis (HP) [13], autoimmune ILDs such as rheumatoid arthritis-associated ILD [14] and systemic sclerosis-associated ILD [15], sarcoidosis [16] and occupation-associated lung disease [17]. Similar to IPF, a decline in forced vital capacity (FVC) is predictive of mortality in patients with these other fibrosing ILDs [18-22]. Given their clinical and pathophysiological similarities, and the rarity of the individual diseases, it has been proposed that fibrosing ILDs with a progressive phenotype be “lumped” together for the purposes of investigating certain potential therapies [3, 23, 24].

Nintedanib is an intracellular inhibitor of tyrosine kinases [10, 25]. In the two INPULSIS trials in patients with IPF, nintedanib reduced the rate of decline in FVC (mL/year) over 52 weeks by about 50% compared to placebo [26]. Recently, the efficacy and safety of nintedanib in subjects with a variety of ILD diagnoses other than IPF, grouped based on the progressive clinical behaviour of their fibrosing ILD despite management deemed appropriate in clinical practice, were investigated in the INBUILD trial. The results showed that, as in the INPULSIS trials, nintedanib reduced the rate of decline in FVC (mL/year) over 52 weeks by about 50% compared to placebo [27]. We used data from subjects who received placebo in the INBUILD and INPULSIS trials to investigate the natural history of progressive fibrosing ILDs. Specifically, we wanted to compare the clinical course of IPF and other progressive fibrosing ILDs, explore whether specific ILD diagnoses were associated with different rates of progression, and investigate whether a relative decline in FVC was associated with mortality in patients with IPF and other progressive fibrosing ILDs.

Materials and methods

Trial design

The two INPULSIS trials and the INBUILD trial were randomised, double-blind, placebo-controlled trials with a 52-week treatment period. The trial designs have been described and the trial protocols are publicly available [26, 27]. The trials were carried out in compliance with the principles of the Declaration of Helsinki and the Harmonised Tripartite Guideline for Good Clinical Practice of the International Conference on Harmonisation, and were approved by the local authorities. Subjects provided written informed consent before trial entry. In all these trials, the primary endpoint was the annual rate of decline in FVC (mL/year), assessed over 52 weeks.

INPULSIS trials

Briefly, subjects in the INPULSIS trials were aged ≥40 years and had a clinical diagnosis of IPF. To be eligible for inclusion based on an HRCT scan (taken within the previous ≤12 months), patients had to have a UIP-like fibrotic pattern defined as meeting criteria A, B and C, A and C, or B and C defined as follows: A, definite honeycomb lung destruction with basal and peripheral predominance; B, presence of reticular abnormality and traction bronchiectasis consistent with fibrosis with basal and peripheral predominance; C, atypical features are absent, specifically nodules and consolidation. Ground glass opacity, if present, had to be less extensive than reticular opacity pattern. Subjects had an FVC ≥50% predicted and a diffusing capacity of the lungs for carbon monoxide (DLco) ≥30 and <80% predicted. There were no inclusion criteria regarding longitudinal disease behaviour. Subjects were randomised 3:2 to receive nintedanib or placebo.

INBUILD trial

Subjects in the INBUILD trial were aged ≥18 years and had a fibrosing ILD other than IPF diagnosed by the investigator according to their usual clinical practice. Patients with IPF were actively excluded. For every subject, the investigator documented an ILD diagnosis on the case report form based on the following nine options: iNSIP, unclassifiable IIP, HP, RA-ILD, mixed connective tissue disease-ILD (MCTD-ILD), SSc-ILD, exposure-related ILD, sarcoidosis, and other fibrosing ILD. Subjects had features of fibrosing lung disease (reticular abnormality with traction bronchiectasis with or without honeycombing) of >10% extent on an HRCT scan (taken within the previous ≤12 months), confirmed by central review, FVC ≥45% predicted and DLco ≥30 and <80% predicted.

Subjects had to meet one of the following criteria for disease progression, in the 24 months before screening, as determined by the investigator, despite management as deemed appropriate in clinical practice for the individual ILD: a relative decline in FVC ≥10% of the predicted value; a relative decline in FVC ≥5–<10% of the predicted value and worsened respiratory symptoms; a relative decline in FVC ≥5–<10% of the predicted value and increased extent of fibrosis on HRCT; worsened respiratory symptoms and increased extent of fibrosis on HRCT.

Subjects were randomised 1:1 to receive nintedanib or placebo. Randomisation was stratified according to the fibrotic pattern on HRCT (UIP-like fibrotic pattern or other fibrotic patterns). The criteria used to identify a UIP-like fibrotic pattern on HRCT in the INBUILD trial were the same as the criteria used in the INPULSIS trials. For each subject, the trial consisted of two parts: Part A, which comprised 52 weeks of treatment, and Part B, a variable treatment period beyond week 52 during which subjects continued to receive blinded treatment until all subjects had completed Part A. Subjects who discontinued treatment were asked to attend all visits as originally planned, including an end-of-treatment visit and a follow-up visit 4 weeks later. The second database lock took place after all patients had completed the follow-up visit or had entered the open-label extension study. The protocol did not allow for use of azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, rituximab, cyclophosphamide, or oral corticosteroids >20 mg/day at randomisation, but initiation of these medications was allowed after 6 months of study treatment in cases of clinically significant deterioration of ILD or connective tissue disease, at the discretion of the investigator.

Analyses

The course of ILD was assessed in subjects who received placebo in the INBUILD and INPULSIS trials. The following were used as measures of longitudinal disease behaviour: annual rate of decline in FVC (mL/year), observed absolute change from baseline in FVC (mL) over time, the proportions of subjects with relative declines in FVC of >5% predicted and >10% predicted at week 52, and all-cause mortality.

To address the question of similarity between IPF and other fibrosing ILDs with a progressive phenotype, data from the placebo group in the overall population in the INBUILD trial were compared with pooled data from the placebo groups of the INPULSIS trials. In addition, the subgroups of subjects with a UIP-like fibrotic pattern on HRCT and with other fibrotic patterns on HRCT in the INBUILD trial were compared with patients with IPF in the INPULSIS trials.

To assess whether specific ILD diagnoses were associated with different rates of progression, the course of ILD in the placebo group of the INBUILD trial was assessed in the following 5 diagnostic groups: iNSIP, unclassifiable IIP, HP, autoimmune ILDs (RA-ILD, SSc-ILD, MCTD-ILD, plus subjects with an autoimmune disease noted in the “Other fibrosing ILDs” category of the case report form) and other ILDs (sarcoidosis, exposure-related ILDs and selected diagnoses from “Other fibrosing ILDs”). Nominal p-values for subgroup-by-time interaction were obtained from tests of heterogeneity across all the diagnostic groups, with no adjustment for multiplicity.

The annual rate of decline in FVC (mL/year) was analysed using a similar random coefficient regression model (with random slopes and intercepts) as was used in the primary analysis of the INBUILD trial, including baseline FVC (mL) and patient population (IPF vs non-IPF) as covariates. The analysis was based on all measurements obtained over the first 52 weeks, including those from subjects who had prematurely discontinued placebo. The model allowed for missing data assuming that they were missing at random. In this paper, we present results that are representative of an “average” subject within the depicted comparison. To evaluate time to death, a log-rank test was utilised and included patient population (IPF vs non-IPF) as a covariate. A Cox proportional hazards model was used to derive the hazard ratio (HR) and 95% confidence interval (CI) between the patient populations (IPF vs non-IPF). Categorical relative declines in FVC % predicted were evaluated using a logistic regression model adjusting for the continuous covariate baseline FVC % predicted and for the patient population (IPF vs non-IPF). Adjusted odds ratios with 95% CIs were used to quantify the effects within each patient population. Subjects with missing data at week 52 were counted as having relative declines in FVC of >5% or >10% predicted, representing a “worst case” analysis.

To explore the question of whether a relative decline in FVC >10% predicted was associated with mortality, we analysed the relationship between a relative decline in FVC of >10% predicted and time to death over 52 weeks in the INBUILD trial and in the INPULSIS trials, and using data up to the second database lock in the INBUILD trial. Evaluations regarding the association of FVC decline with mortality were based on a Cox proportional hazards model where time to FVC decline >10% predicted was included as a time-dependent variable, using the programming statements method [28]. The assessment in the overall population in the INBUILD trial also included the stratification variable (UIP-like fibrotic pattern versus other fibrotic patterns on HRCT). No other variables were included in these evaluations.

Results

Subjects

The baseline characteristics of subjects in the placebo groups of the INBUILD trial (n=331) and INPULSIS trials (n=423) are summarised in Table 1. At baseline, mean FVC % predicted was lower in the INBUILD trial than in the INPULSIS trials (69% vs 79%).

Annual rate of decline in FVC

The adjusted mean annual rate of decline in FVC over 52 weeks in the placebo group of the overall population in the INBUILD trial was similar to that observed in the placebo group of the INPULSIS trials (−192.9 mL/year and −221.0 mL/year, respectively; nominal p-value: 0.19) (Figure 1). Subjects with a UIP-like fibrotic pattern on HRCT in the INBUILD trial also had an adjusted annual rate of decline similar to that observed in the INPULSIS trials (−214.6 mL/year and −223.2 mL/year, respectively; nominal p-value: 0.74) (Figure 1). The adjusted annual rate of decline in FVC in subjects with other fibrotic patterns on HRCT in the INBUILD trial was lower than that observed in the INPULSIS trials (−160.1 mL/year versus −224.1 mL/year; nominal p-value: 0.032) (Figure 1). The curves of observed change from baseline in FVC (mL) over 52 weeks in the INBUILD and INPULSIS trials had similar trajectories (Figure 2).

In the INBUILD trial, the annual rate of decline in FVC was similar across the 5 pre-specified groups by ILD diagnosis; in all the subgroups, subjects with a UIP-like fibrotic pattern on HRCT had a numerically greater annual rate of decline in FVC than those with other fibrotic patterns on HRCT (Figure 3).

Proportions of subjects who had categorical relative declines in FVC % predicted

The proportions of subjects who had relative declines from baseline in FVC >10% or >5% predicted at week 52 were similar between the INBUILD and INPULSIS trials (Figures 4A and 4B). A relative decline in FVC >10% predicted at week 52 was observed in 48.9% of the overall population in the INBUILD trial and 48.7% of subjects in the INPULSIS trials. In the INBUILD trial, a relative decline in FVC >10% predicted at week 52 was observed in a greater proportion of subjects with a UIP-like fibrotic pattern on HRCT than in those with other fibrotic patterns (52.4% vs 43.2%) (Figure 4A). A relative decline in FVC >5% predicted at week 52 was observed in 68.6% of the overall population in the INBUILD trial and 64.5% of subjects in the INPULSIS trials (Figure 4B). In the INBUILD trial, the proportion of subjects with a relative

decline in FVC >5% predicted at week 52 was similar in subjects with a UIP-like fibrotic pattern on HRCT and in those with other fibrotic patterns (70.4% and 65.6%) (Figure 4B).

Mortality and its association with relative decline in FVC >10% predicted

Over 52 weeks, deaths occurred in 34 (5.1%) of subjects in the INBUILD trial and 33 (7.8%) of subjects in the INPULSIS trials. Compared with the INPULSIS trials, the proportion of subjects who died over 52 weeks was similar in the overall population and in subjects with a UIP-like fibrotic pattern in the INBUILD trial, and lower in those with other fibrotic patterns on HRCT in the INBUILD trial (HR vs INPULSIS 0.63, 0.97 and 0.10, respectively) (Table 2).

In the INBUILD trial, a relative decline in FVC of >10% predicted was associated with an increased risk of death over 52 weeks in the overall population and in subjects with UIP-like pattern on HRCT (HR 3.64 and 3.35, respectively). A similar association was observed in the INPULSIS trials (HR: 3.95) (Table 3). As only one death occurred over 52 weeks in subjects with other fibrotic patterns on HRCT in the INBUILD trial, the HR could not be calculated. Using data up to the second database lock (median follow-up: approximately 19 months), a relative decline in FVC of >10% predicted was associated with an increased risk of death in the overall population (HR: 3.48)and in subjects with a UIP-like fibrotic pattern on HRCT (HR: 3.64). A similar trend was observed in subjects with other fibrotic patterns on HRCT (HR: 2.88) (Table 4).

Discussion

We used data from the placebo groups of the INBUILD and INPULSIS trials to investigate the natural history of progressive fibrosing ILDs. We found that subjects in the INBUILD trial, who had diagnoses of a fibrosing ILD other than IPF and met criteria for ILD progression in the previous 24 months based on decline in lung function or worsening of symptoms and fibrotic changes on HRCT, despite management deemed appropriate in clinical practice, had a disease course similar to that of subjects with IPF.Rates of FVC decline and mortality over 52 weeks were comparable between the INBUILD and INPULSIS trials.

Previous studies have suggested that in patients with fibrosing ILDs, the presence of a UIP-like fibrotic pattern on HRCT is associated with more rapid disease progression [11, 29-32]. Consistent with these findings, in the INBUILD trial, the rate of FVC decline and mortality over 52 weeks were greater in subjects with a UIP-like fibrotic pattern on HRCT than in subjects with other fibrotic patterns. That said, the rate of FVC decline in subjects with other fibrotic patterns

on HRCT (160 mL/year) was dramatic, with almost 50% of these subjects showing a relative decline in FVC >10% predicted over 52 weeks, similar to patients with IPF.

Although the INBUILD trial was not designed or powered to study the effects of nintedanib in patients with specific ILD diagnoses, our results suggest that in subjects who had >10% extent of fibrosis on HRCT and clinical signs of progression despite management, the rate of decline in FVC was similar across subgroups with different diagnoses. This suggests that, although it is critical that patients receive an accurate diagnosis of ILD at the time of presentation to inform optimal management, observation of disease behaviour can identify a population of patients who develop a progressive fibrosing phenotype despite treatment and are therefore at high risk of further progression.

Declines in FVC of >10% and >5% predicted have been associated with mortality in patients with IPF [33, 34] and other chronic fibrosing ILDs [19-22]. The subjects enrolled in the INBUILD trial met protocol-defined criteria for progression of ILD in the two years before screening. The subjects with IPF enrolled in the INPULSIS trials were not required to meet criteria for disease progression to enter the trial, as IPF is, by definition, a progressive disease [1]. In both the INBUILD and INPULSIS trials, approximately half the subjects in the placebo group had a relative decline in FVC of >10% predicted and two-thirds had a relative decline of >5% predicted over 52 weeks. In the INBUILD trial, a relative decline in FVC of >10% predicted was associated with a more than three-fold increase in the risk of death over 52 weeks, both in the overall population and in subjects with a UIP-like fibrotic pattern on HRCT, comparable to what was observed in the INPULSIS trials. Over a longer observation period, this association also became apparent in subjects with other fibrotic patterns on HRCT. These data suggest that, similar to IPF, a decline in FVC is associated with an increased risk of early death in patients with non-IPF fibrosing ILDs that have progressed despite management.

Previous analyses of the INBUILD trial have shown that the effect of nintedanib versus placebo on the rate of FVC decline was consistent across subpopulations by HRCT pattern [27] and by ILD diagnosis [35]. Combined with our current results, these findings provide further support for a progressive fibrosing phenotype in ILD, characterised by progressive decline in lung function and early mortality, irrespective of the underlying ILD diagnosis and fibrotic pattern on HRCT. These findings also support the “lumping” of patients with progressive fibrosing ILDs for the purposes of investigating certain therapies for these rare diseases, as has previously been proposed [3].

In conclusion, our findings show that the subjects with non-IPF progressive fibrosing ILDs who received placebo in the INBUILD trial had a clinical course similar to patients with untreated IPF, irrespective of underlying ILD diagnosis or the fibrotic pattern on HRCT. Patients with fibrosing ILDs other than IPF who have shown progression of ILD in the past 24 months, despite management deemed appropriate in clinical practiceare at high risk of further ILD progression and early mortality.

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Conflict of interest

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Author contributions

KKB, AUW, SLFW, RSH, ECB, KT, and VC were involved in the design of the study. RGG was involved in data analysis. All authors were involved in the interpretation of the data and in the writing and critical review of the manuscript.

References

1. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, Behr J, Cottin V, Danoff SK, Morell F, Flaherty KR, Wells A, Martinez FJ, Azuma A, Bice TJ, Bouros D, Brown KK, Collard HR, Duggal A, Galvin L, Inoue Y, Jenkins RG, Johkoh T, Kazerooni EA, Kitaichi M, Knight SL, Mansour G, Nicholson AG, Pipavath SNJ, Buendía-Roldán I, Selman M, Travis WD, Walsh S, Wilson KC; American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med 2018; 198: e44–e68.
2. Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, Ryerson CJ, Ryu JH, Selman M, Wells AU, Behr J, Bouros D, Brown KK, Colby TV, Collard HR, Cordeiro CR, Cottin V, Crestani B, Drent M, Dudden RF, Egan J, Flaherty K, Hogaboam C, Inoue Y, Johkoh T, Kim DS, Kitaichi M, Loyd J, Martinez FJ, Myers J, Protzko S, Raghu G, Richeldi L, Sverzellati N, Swigris J, Valeyre D; ATS/ERS Committee on Idiopathic Interstitial Pneumonias. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2013; 188: 733–748.
3. Wells AU, Brown KK, Flaherty KR, Kolb M, Thannickal VJ; IPF Consensus Working Group. What's in a name? That which we call IPF, by any other name would act the same. Eur Respir J 2018;51(5). pii :1800692.
4. Cottin V, Wollin L, Fischer A, Quaresma M, Stowasser S, Harari S. Fibrosing interstitial lung diseases: knowns and unknowns. Eur Respir Rev 2019; 28(151). pii: 180100.
5. Kolb M, Vašáková M. The natural history of progressive fibrosing interstitial lung diseases. Respir Res 2019; 20: 57. doi: 10.1186/s12931-019-1022-1.
6. Thannickal VJ, Toews GB, White ES, Lynch JP 3rd, Martinez FJ. Mechanisms of pulmonary fibrosis. Annu Rev Med 2004; 55: 395–417.
7. Prasse A, Pechkovsky DV, Toews GB, Schäfer M, Eggeling S, Ludwig C, Germann M, Kollert F, Zissel G, Müller-Quernheim J. CCL18 as an indicator of pulmonary fibrotic activity in idiopathic interstitial pneumonias and systemic sclerosis. Arthritis Rheum 2007; 56: 1685-93.
8. Bagnato G, Harari S. Cellular interactions in the pathogenesis of interstitial lung diseases. Eur Respir Rev 2015; 24: 102–114.

9. Luckhardt TR, Thannickal VJ. Systemic sclerosis-associated fibrosis: an accelerated aging phenotype? Curr Opin Rheumatol 2015; 27: 571–576.

10. Wollin L, Distler JHW, Redente EF, Riches DWH, Stowasser S, Schlenker-Herceg R, Maher TM, Kolb M. Potential of nintedanib in treatment of progressive fibrosing interstitial lung diseases. Eur Respir J 2019; 54(3). pii: 1900161.

11. Kim EJ, Elicker BM, Maldonado F, Webb WR, Ryu JH, Van Uden JH, Lee JS, King TE Jr, Collard HR. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J 2010; 35: 1322–1328.

12. Guler SA, Ellison K, Algamdi M, Collard HR, Ryerson CJ. Heterogeneity in unclassifiable interstitial lung disease. A systematic review and meta-analysis. Ann Am Thorac Soc 2018; 15: 854–863.

13. De Sadeleer LJ, Hermans F, de Dycker E, Yserbyt J, Verschakelen JA, Verbeken EK, Verleden GM, Wuyts WA. Effects of corticosteroid treatment and antigen avoidance in a large hypersensitivity pneumonitis cohort: a single-centre cohort study. J Clin Med 2018; 8(1). pii: E14.

14. Doyle TJ, Dellaripa PF. Lung manifestations in the rheumatic diseases. Chest 2017; 152: 1283–95.

15. Guler SA, Winstone TA, Murphy D, Hague C, Soon J, Sulaiman N, Li KH, Dunne J, Wilcox PG, Ryerson CJ. Does systemic sclerosis-associated interstitial lung disease burn out? Specific phenotypes of disease progression. Ann Am Thorac Soc 2018; 15: 1427–33.

16. Walsh SL, Wells AU, Sverzellati N, Keir GJ, Calandriello L, Antoniou KM, Copley SJ, Devaraj A, Maher TM, Renzoni E, Nicholson AG, Hansell DM. An integrated clinicoradiological staging system for pulmonary sarcoidosis: a case-cohort study. Lancet Respir Med 2014; 2: 123–30.

17. Khalil N, Churg A, Muller N, O'Connor R. Environmental, inhaled and ingested causes of pulmonary fibrosis. Toxicol Pathol 2007; 35:86–96.

18. Jegal Y, Kim DS, Shim TS, Lim CM, Do Lee S, Koh Y, Kim WS, Kim WD, Lee JS, Travis WD, Kitaichi M, Colby TV. Physiology is a stronger predictor of survival of pathology in fibrotic interstitial pneumonia. Am J Respir Crit Care Med 2005; 171: 639–644.

19. Solomon JJ, Chung JH, Cosgrove GP, Demoruelle MK, Fernandez-Perez ER, Fischer A, Frankel SK, Hobbs SB, Huie TJ, Ketzer J, Mannina A, Olson AL, Russell G, Tsuchiya Y,

Yunt ZX, Zelarney PT, Brown KK, Swigris JJ. Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J 2016; 47: 588–596.

20. Gimenez A, Storrer K, Kuranishi L, Soares MR, Ferreira RG, Pereira CAC. Change in FVC and survival in chronic fibrotic hypersensitivity pneumonitis. Thorax 2017; 73: 391–392.
21. Goh NS, Hoyles RK, Denton CP, Hansell DM, Renzoni EA, Maher TM, Nicholson AG, Wells AU. Short-term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. Arthritis Rheumatol 2017; 69: 1670-78.
22. Volkmann ER, Tashkin DP, Sim M, Li N, Goldmuntz E, Keyes-Elstein L, Pinckney A, Furst DE, Clements PJ, Khanna D, Steen V, Schraufnagel DE, Arami S, Hsu V, Roth MD, Elashoff RM, Sullivan KM; SLS I and SLS II study groups. Short-term progression of interstitial lung disease in systemic sclerosis predicts long-term survival in two independent clinical trial cohorts. Ann Rheum Dis 2019; 78: 122–130.
23. Flaherty KR, Brown KK, Wells AU, Clerisme-Beaty E, Collard HR, Cottin V, Devaraj A, Inoue Y, Le Maulf F, Richeldi L, Schmidt H, Walsh S, Mezzanotte W, Schlenker-Herceg R. Design of the PF-ILD trial: a double-blind, randomised, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease. BMJ Open Respir Res 2017; 4: e000212.
24. Torrisi SE, Kahn N, Wälscher J, Sarmand N, Polke M, Lars K, Eichinger M, Heussel CP, Palmucci S, Sambataro FM, Sambataro G, Sambataro D, Vancheri C, Kreuter M. Possible value of antifibrotic drugs in patients with progressive fibrosing non-IPF interstitial lung diseases. BMC Pulm Med. 2019; 19(1): 213.
25. Wollin L, Wex E, Pautsch A, Schnapp G, Hostettler KE, Stowasser S, Kolb M. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. Eur Respir J 2015; 45: 1434–1445.
26. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, Cottin V, Flaherty KR, Hansell DM, Inoue Y, Kim DS, Kolb M, Nicholson AG, Noble PW, Selman M, Taniguchi H, Brun M, Le Maulf F, Girard M, Stowasser S, Schlenker-Herceg R, Disse B, Collard HR; INPULSIS trial investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014; 370: 2071–2082.
27. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, Richeldi L, Kolb M, Tetzlaff K, Stowasser S, Coeck C, Clerisme-Beaty E, Rosenstock B, Quaresma M, Haeufel T,

Goeldner RG, Schlenker-Herceg R, Brown KK; INBUILD trial investigators. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med 2019; 381: 1718–1727.

28. SAS Institute Inc. 2018. SAS/STAT® 15.1 User's Guide. Cary, NC: SAS Institute Inc. Available at: https://support.sas.com/documentation/onlinedoc/stat/151/spp.pdf
29. Walsh SL, Sverzellati N, Devaraj A, Keir GJ, Wells AU, Hansell DM. Connective tissue disease related fibrotic lung disease: high resolution computed tomographic and pulmonary function indices as prognostic determinants. Thorax 2014; 69: 216–222.
30. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Progressive decline of lung function in rheumatoid arthritis-associated interstitial lung disease. Arthritis Rheumatol 2017; 69: 542–549.
31. Salisbury ML, Gu T, Murray S, Gross BH, Chughtai A, Sayyouh M, Kazerooni EA, Myers JL, Lagstein A, Konopka KE, Belloli EA, Sheth JS, White ES, Holtze C, Martinez FJ, Flaherty KR. Hypersensitivity pneumonitis: radiologic phenotypes are associated with distinct survival time and pulmonary function trajectory. Chest 2019; 155: 699–711.
32. Adegunsoye A, Oldham JM, Bellam SK, Montner S, Churpek MM, Noth I, Vij R, Strek ME, Chung JH. Computed tomography honeycombing identifies a progressive fibrotic phenotype with increased mortality across diverse interstitial lung diseases. Ann Am Thorac Soc 2019; 16: 580–588.
33. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, King TE Jr, Lancaster L, Noble PW, Sahn SA, Thomeer M, Valeyre D, Wells AU. Forced vital capacity in patients with idiopathic pulmonary fibrosis. Test properties and minimal clinically important difference. Am J Respir Crit Care Med 2011; 184:1382–89.
34. Richeldi L, Ryerson CJ, Lee JS, Wolters PJ, Koth LL, Ley B, Elicker BM, Jones KD, King TE Jr, Ryu JH, Collard HR. Relative versus absolute change in forced vital capacity in idiopathic pulmonary fibrosis. Thorax 2012; 67: 407-11.
35. Wells AU, Flaherty KR, Brown KK, Inoue Y, Devaraj A, Richeldi L, Moua T, Crestani B, Wuyts WA, Stowasser S, Quaresma M, Goeldner R, Schlenker-Herceg R, Kolb M. Nintedanib in patients with progressive fibrosing interstitial lung diseases: subgroup analyses by interstitial lung disease diagnosis in the randomised, placebo-controlled INBUILD trial. Lancet Respir Med; in press.

TABLE 1. Baseline characteristics of subjects in the INBUILD and INPULSIS trials.

	INBUILD trial (overall population)		INPULSIS trials (pooled)	
	Nintedanib (n=332)	**Placebo (n=331)**	**Nintedanib (n=638)**	**Placebo (n=423)**
Male, n (%)	179 (53.9)	177 (53.5)	507 (79.5)	334 (79.0)
Age, years, mean (SD)	65.2 (9.7)	66.3 (9.8)	66.6 (8.1)	67.0 (7.9)
Former or current smoker, n (%)	169 (50.9)	169 (51.1)	464 (72.7)	301 (71.2)
FVC, mL, mean (SD)	2340 (740)	2321 (728)	2714 (757)	2728 (810)
FVC, % predicted, mean (SD)	68.7 (16.0)	69.3 (15.2)	79.7 (17.6)	79.3 (18.2)
DLco, % predicted, mean (SD)*	44.4 (11.9)	47.9 (15.0)	47.4 (13.5)	47.0 (13.4)

*Corrected for haemoglobin level. DLco, diffusion capacity of the lungs for carbon monoxide; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.

TABLE 2. Proportion of subjects who died over 52 weeks in the placebo groups of the INBUILD and INPULSIS trials.

	INBUILD trial			INPULSIS trials (n=423)
	Overall population (n=331)	**UIP-like fibrotic pattern on HRCT (n=206)**	**Other fibrotic patterns on HRCT (n=125)**	
Deaths over 52 weeks, n (%)	17 (5.1)	16 (7.8)	1 (0.8)	33 (7.8)
Hazard ratio vs INPULSIS trials (95% CI)*	0.63 (0.35, 1.13)	0.97 (0.53, 1.76)	0.10 (0.01, 0.70)	
Nominal p-value†	0.12	0.92	0.004	

*Based on a Cox regression model with terms for patient population (IPF vs non-IPF). †Based on a log−rank test.

HRCT, high resolution computed tomography; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia.

TABLE 3. Relationship between relative decline in FVC >10% predicted and time to death over 52 weeks in the placebo group of the INBUILD and INPULSIS trials.

	INBUILD trial*		**INPULSIS trials**
	Overall population (n=331)	**UIP-like fibrotic pattern on HRCT (n=206)**	**(n=423)**
Deaths over 52 weeks, n (%)	17 (5.1)	16 (7.8)	33 (7.8)
Relationship between relative decline in FVC >10% predicted and time to death			
Hazard ratio (95% CI)[†]	3.64 (1.29, 10.28)	3.35 (1.16, 9.64)	3.95 (1.87, 8.33)
p-value[‡]	0.015	0.025	<0.001

*As the number of subjects with other fibrotic patterns on HRCT who died was 1, the relationship between a relative decline in FVC >10% predicted and mortality could not be analysed. [†]Based on Cox regression model with relative decline in FVC >10% predicted as a time-dependent variable. [‡]Based on Wald test. FVC, forced vital capacity; HRCT, high resolution computed tomography; UIP, usual interstitial pneumonia.

TABLE 4. Relationship between relative decline in FVC >10% predicted and time to death up to the second database lock* in the placebo group of the INBUILD trial.

	Overall population (n=331)	**Subjects with UIP-like fibrotic pattern on HRCT (n=206)**	**Subjects with other fibrotic patterns on HRCT (n=125)**
Deaths up to second database lock, n (%)	45 (13.6)	36 (17.5)	9 (7.2)
Relationship between relative decline in FVC >10% predicted and time to death			
Hazard ratio (95% CI)[†]	3.48 (1.71, 7.10)	3.64 (1.65, 8.06)	2.88 (0.59, 14.09)
p-value[‡]	<0.001	0.001	0.192

*The second database lock took place after all patients had completed the follow-up visit or had entered the open-label extension study; the median follow-up was approximately 19 months. Analyses over a similar time period in the INPULSIS trials was not possible as they were 52-week trials. [†]Based on Cox regression model with relative decline in FVC >10% predicted as a time-dependent variable. The assessment in the overall population also included the stratification variable (UIP-like fibrotic pattern versus other fibrotic patterns on HRCT). [‡]Based on Wald test. FVC, forced vital capacity; HRCT, high resolution computed tomography; UIP, usual interstitial pneumonia.

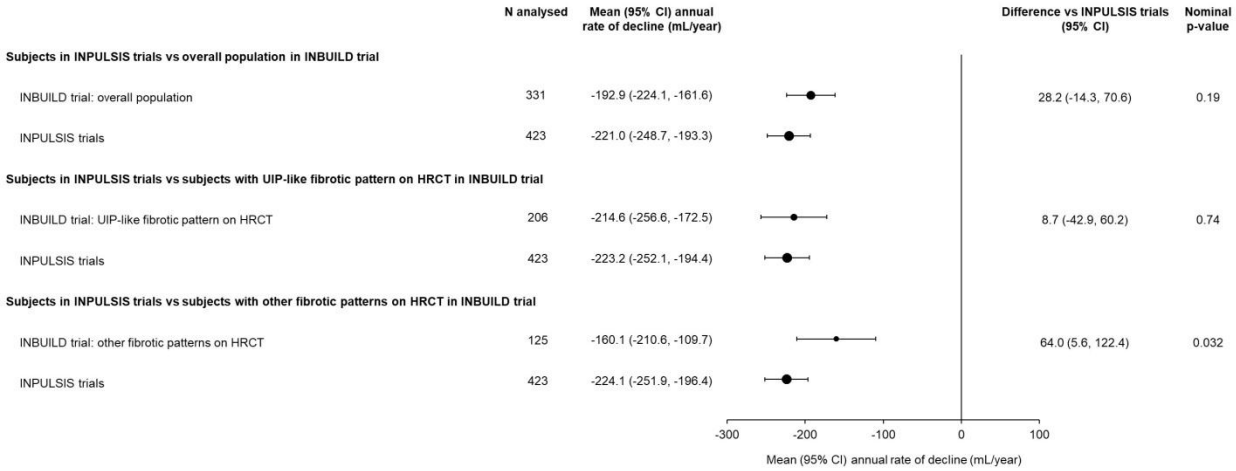
FIGURE LEGENDS

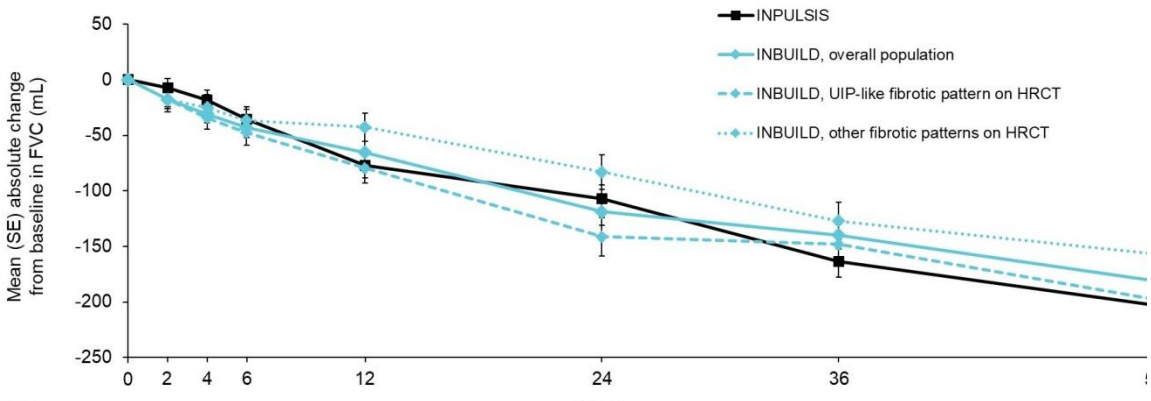
FIGURE 1. Annual rate of decline in FVC (mL/year) over 52 weeks in the placebo groups of the INBUILD and INPULSIS trials. The adjusted mean rate of decline in FVC depicted here is representative of an "average" patient within the depicted comparison. The baseline FVC value was computed as the mean baseline FVC of all the subjects from the INBUILD and INPULSIS trials that were used in the respective comparison. FVC, forced vital capacity; HRCT, high resolution computed tomography; UIP, usual interstitial pneumonia.

FIGURE 2. Observed change from baseline over 52 weeks in FVC in the placebo groups of the INPULSIS and INBUILD trials. FVC, forced vital capacity; HRCT, high resolution computed tomography; UIP, usual interstitial pneumonia.

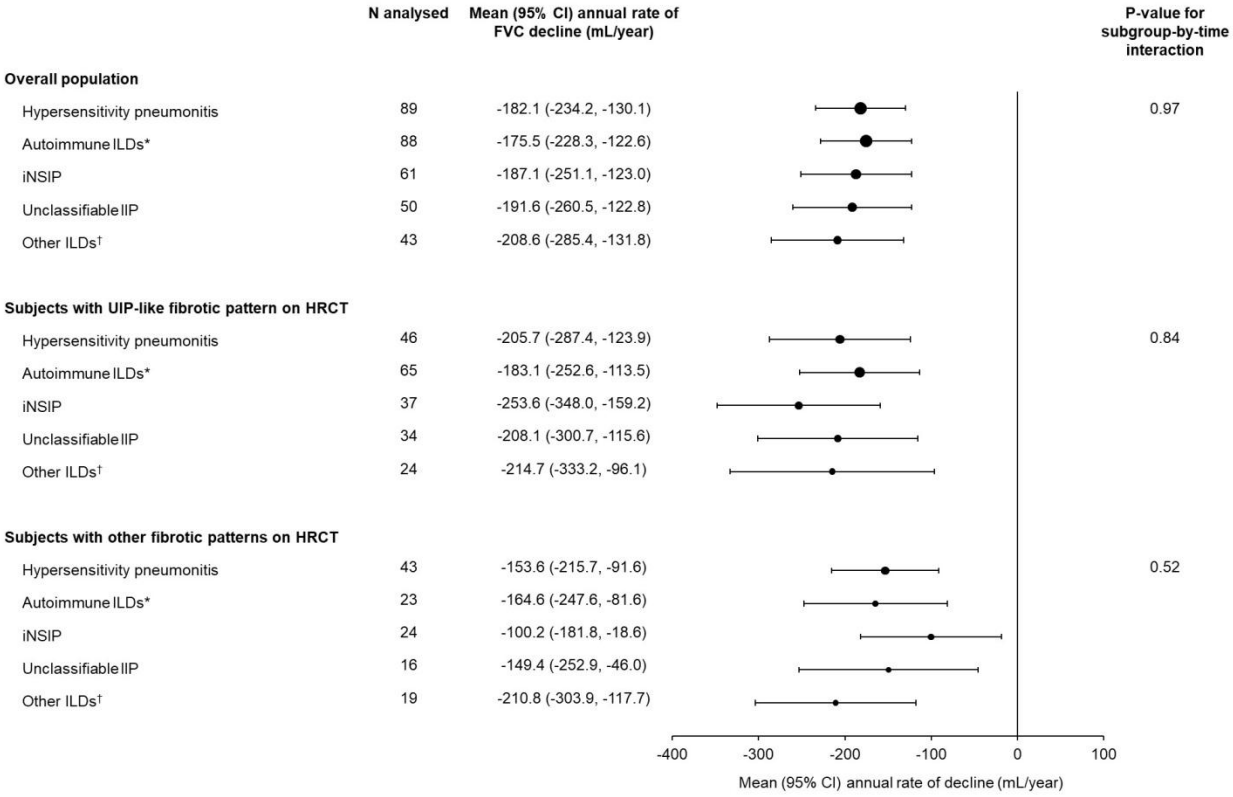
FIGURE 3. Annual rate of decline in FVC (mL/year) over 52 weeks in the placebo groups of the INBUILD trial by ILD diagnosis. *Autoimmune ILDs: RA-ILD, SSc-ILD, MCTD-ILD, plus autoimmune ILDs in "Other fibrosing ILDs". †Other ILDs: sarcoidosis, exposure-related ILDs and other terms in "Other fibrosing ILDs". FVC, forced vital capacity; HRCT, high resolution computed tomography; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; iNSIP, idiopathic non-specific interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; MCTD, mixed connective tissue disease; RA, rheumatoid arthritis; SSc, systemic sclerosis; UIP, usual interstitial pneumonia.

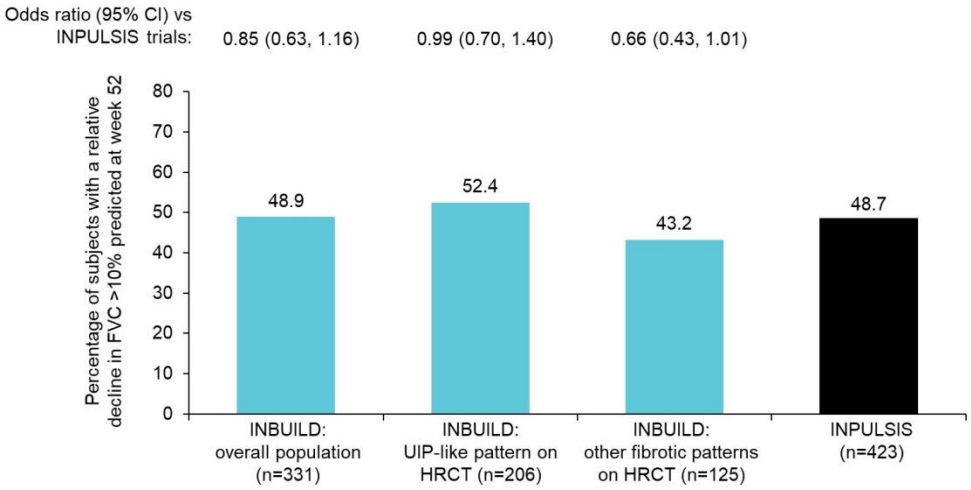
FIGURE 4. Proportion of subjects who had (A) a relative decline in FVC >10% predicted at week 52 and (B) a relative decline in FVC >5% predicted at week 52 in the placebo groups of the INPULSIS and INBUILD trials. FVC, forced vital capacity; HRCT, high resolution computed tomography; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia.

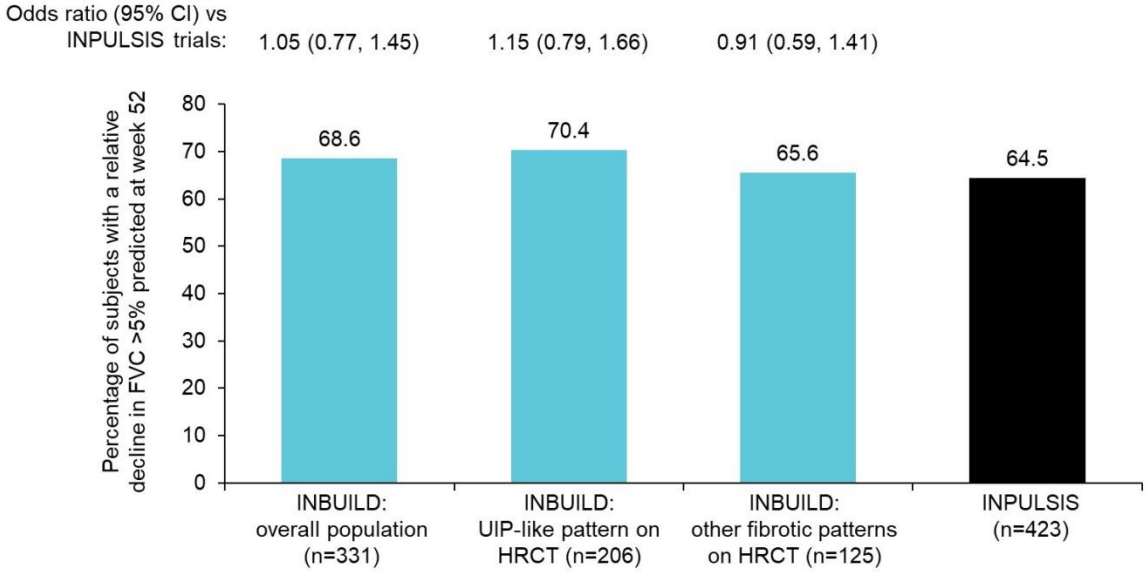

N analysed
Mean (95% CI) annual rate of decline (mL/year)
Difference vs INPULSIS trials (95% CI)
Nominal p-value
Subjects in INPULSIS trials vs overall population in INBUILD trial
INBUILD trial: overall population
331
-192.9 (-224.1, -161.6)
28.2 (-14.3, 70.6)
0.19
INPULSIS trials
423
-221.0 (-248.7, -193.3)
Subjects in INPULSIS trials vs subjects with UIP-like fibrotic pattern on HRCT in INBUILD trial
INBUILD trial: UIP-like fibrotic pattern on HRCT
206
-214.6 (-256.6, -172.5)
8.7 (-42.9, 60.2)
0.74
INPULSIS trials
423
-223.2 (-252.1, -194.4)
Subjects in INPULSIS trials vs subjects with other fibrotic patterns on HRCT in INBUILD trial
INBUILD trial: other fibrotic patterns on HRCT
125
-160.1 (-210.6, -109.7)
64.0 (5.6, 122.4)
0.032
INPULSIS trials
423
-224.1 (-251.9, -196.4)
-300
-200
-100
0
100
Mean (95% CI) annual rate of decline (mL/year)



No. of subjects							
INPULSIS	417	408	407	403	395	383	3
INBUILD, overall population	325	326	325	320	311	296	2
INBUILD, UIP-like fibrotic pattern	202	202	201	197	190	176	1
INBUILD, other fibrotic patterns	123	124	124	123	121	120	1


N analysed
Mean (95% CI) annual rate of FVC decline (mL/year)
P-value for subgroup-by-time interaction
Overall population
Hypersensitivity pneumonitis 89 -182.1 (-234.2, -130.1) 0.97
Autoimmune ILDs* 88 -175.5 (-228.3, -122.6)
iNSIP 61 -187.1 (-251.1, -123.0)
Unclassifiable IIP 50 -191.6 (-260.5, -122.8)
Other ILDs† 43 -208.6 (-285.4, -131.8)
Subjects with UIP-like fibrotic pattern on HRCT
Hypersensitivity pneumonitis 46 -205.7 (-287.4, -123.9) 0.84
Autoimmune ILDs* 65 -183.1 (-252.6, -113.5)
iNSIP 37 -253.6 (-348.0, -159.2)
Unclassifiable IIP 34 -208.1 (-300.7, -115.6)
Other ILDs† 24 -214.7 (-333.2, -96.1)
Subjects with other fibrotic patterns on HRCT
Hypersensitivity pneumonitis 43 -153.6 (-215.7, -91.6) 0.52
Autoimmune ILDs* 23 -164.6 (-247.6, -81.6)
iNSIP 24 -100.2 (-181.8, -18.6)
Unclassifiable IIP 16 -149.4 (-252.9, -46.0)
Other ILDs† 19 -210.8 (-303.9, -117.7)
-400
-300
-200
-100
0
100
Mean (95% CI) annual rate of decline (mL/year)


Odds ratio (95% CI) vs INPULSIS trials:
0.85 (0.63, 1.16)
0.99 (0.70, 1.40)
0.66 (0.43, 1.01)
Percentage of subjects with a relative decline in FVC >10% predicted at week 52
80
70
60
50
40
30
20
10
0
48.9
52.4
43.2
48.7
INBUILD: overall population (n=331)
INBUILD: UIP-like pattern on HRCT (n=206)
INBUILD: other fibrotic patterns on HRCT (n=125)
INPULSIS (n=423)


Odds ratio (95% CI) vs INPULSIS trials:
1.05 (0.77, 1.45)
1.15 (0.79, 1.66)
0.91 (0.59, 1.41)
Percentage of subjects with a relative decline in FVC >5% predicted at week 52
80
70
60
50
40
30
20
10
0
68.6
70.4
65.6
64.5
INBUILD: overall population (n=331)
INBUILD: UIP-like pattern on HRCT (n=206)
INBUILD: other fibrotic patterns on HRCT (n=125)
INPULSIS (n=423)