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Nintedanib for non-IPF progressive pulmonary fibrosis: 12-month outcome data from a real-world multicentre observational study

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ABSTRACT

Background

Nintedanib slows lung function decline for patients with non-IPF progressive pulmonary fibrosis (PPF) in clinical trials, but the real-world safety and efficacy are not known.

Methods

In this retrospective cohort study, standardised data was collected across 8 UK centres from patients in whom nintedanib was initiated for PPF between 2019 and 2020 through an early access programme. Rate of lung function change in the 12 months pre- and post-nintedanib initiation was the primary analysis. Symptoms, drug safety, tolerability, and stratification by interstitial lung disease (ILD) subtype and CT pattern were secondary analyses.

Results

126 patients were included; 67(53%) females, mean age 60(±13) years. At initiation of nintedanib, mean FVC was 1.87L (58%) and DLco 32.7% predicted. 68% of patients were prescribed prednisolone (median dose 10mg) and 69% prescribed a steroid sparing agent. In the 12 months after nintedanib initiation, lung function decline was significantly lower than in the preceding 12 months; FVC -88.8ml vs -239.9mL respectively, (p=0.004) and absolute decline in DLco -2.1% vs -6.1% respectively; (p=0.004). Response to nintedanib was consistent in sensitivity and secondary analyses. 89/126 (71%) of patients reported side effects but 86 of the surviving 108 patients (80%) were still taking nintedanib at 12 months with patients reporting a reduced perception of symptom decline. There were no serious adverse events.

Conclusion

In PPF, the real-world efficacy of nintedanib replicated that of clinical trials, significantly attenuating lung function decline. Despite the severity of disease, nintedanib was safe and well tolerated in this real-world multicentre study.

1. Background

Progressive pulmonary fibrosis (PPF) occurs across a range of interstitial lung diseases (ILDs) including fibrotic hypersensitivity pneumonitis (fHP) and connective tissue disease-associated ILD (CTD-ILD) (1-4). The natural history of PPF mirrors idiopathic pulmonary fibrosis (IPF)(5, 6) ultimately leading to respiratory failure and early mortality(4). It is estimated that 18-40% of patients with ILD develop PPF despite conventional therapy(6-8). The PROGRESS study(6) reported substantial progression of disease in patients with PPF despite 91.4% of patients receiving immunosuppressive therapy, highlighting the urgent need for effective treatment.

Nintedanib, a tyrosine kinase inhibitor(10), slows the annual rate of lung function decline in patients with IPF(11) and most recently in patients with progressive non-IPF fibrosing lung diseases (12, 13).

The INBUILD study and subsequent sub-analyses confirm the antifibrotic efficacy of nintedanib independent of ILD diagnosis once progression despite optimal management has occurred. (12) (14, 15). This study has shown that participants who experience PPF despite conventional management over the preceding 24 months demonstrate subsequent disease progression with the same magnitude of decline as untreated IPF (11, 16, 17).

Whilst there is randomised controlled trial evidence supporting the use of nintedanib for non-IPF PPF (12, 13), the extent to which the benefits observed in trials translates into real-world efficacy, safety and tolerability for patients is unknown.

Nintedanib was offered for the treatment of patients in the United Kingdom with a diagnosis of non-IPF PPF in a national early access programme between May 2019 and August 2020. The aim of this multicentre study was to assess the impact of nintedanib on the clinical course of patients with PPF in a real-world setting.

2. Methods

2.1 Patient population

The study was granted ethical approval (IRAS ID 292810, REC reference 21/LO/0091) and was registered locally at each participating centre. Applications for access to nintedanib were submitted by specialist ILD physicians for eligible patients (≥18 years of age) meeting the following INBUILD criteria for PPF(12) over the preceding 24 months;

- Relative decline in forced vital capacity (FVC) ⩾10%

- Relative decline in FVC of 5% - 10% with worsening respiratory symptoms or increased extent of fibrosis on high resolution CT (HRCT) scan

- Worsening respiratory symptoms and increased extent of fibrosis on HRCT

All applications were centrally reviewed and only approved for patients meeting the above criteria. A case report form (CRF) collected retrospective and prospective data for each patient (Supplementary appendix 1). Lung function data were obtained annually. Other data to suggest clinical worsening, including increasing oxygen requirements were collected as a descriptor within the CRF but were not used to inform eligibility for nintedanib. Participating centres were responsible for monitoring blood tests and documenting adverse events. Data were collected as per clinical practice from electronic patient records by each participating centre and anonymised prior to collation.

2.2 Outcomes and Analyses

The primary outcome measure was the difference in FVC change (millilitres (ml)) in the 12 months (+/- 6 months) post-nintedanib initiation relative to the change in the 12 months (+/- 6 months) pre-initiation of nintedanib. Secondary outcomes were change in the % predicted diffusing capacity of the lungs for carbon monoxide (ppDLco) and ppKco post-initiation relative to pre-initiation. All reported lung function variables were pre-bronchodilator measurements.

Secondary analyses assessed differences in lung function change in individual patient groups (sex, diagnosis and radiological pattern on CT), based on the difference between lung function changes in the preceding and proceeding 12 months from nintedanib initiation.

Change in symptoms of shortness of breath, exercise tolerance and cough at initiation of nintedanib and at 12 months follow up were recorded as worsened, no change, or improved based on clinical review of patient records, and included as an additional secondary outcome. Adverse effects including 12-month mortality and side effects as well as compliance data were collected to ascertain the overall tolerability and safety of nintedanib in this population.

2.3 Statistical methods

Multilevel models for repeat measures were employed to account for all lung function tests recorded across the cohort, restricted linear splines were used to compare rate of change in the year pre- and post-nintedanib with a knot at initiation.

In secondary analyses of between group differences, multilevel models were adjusted for a-priori covariates age, sex, diagnostic group (fHP, CTD-ILD, other), radiological pattern (usual interstitial

pneumonia (UIP) pattern of fibrosis on high resolution CT) and early cessation of nintedanib treatment (prior to 12 months).

Sensitivity analyses were performed using percent predicted FVC (ppFVC), timing of ppFVC from nintedanib initiation as a continuous variable instead of discrete, and three single imputation strategies for missing ppFVC data assumed not missing at random: median imputation at time point, a carried forward or backward rule, and a 10% relative decline imputation. Sensitivity analyses were also performed in a restricted cohort of patients with complete lung function at all three time points, including paired t-test of pre and post changes in lung function, as well as unpaired tests of differences in change between sex, radiological pattern and diagnostic group.

To compare symptom changes at initiation of nintedanib and at follow up after 12 months of treatment, dichotomised categories of 'worse/no change' or 'improved' were included in McNemar's tests on discordant pairs. Relationships between early cessation of nintedanib treatment and patient characteristics were tested using Fisher's exact tests and Wilcoxon rank sum tests. Similar tests were performed to assess for bias in patients with complete lung function. All analyses were performed in Stata SE16, p-value<0.05 was considered significant for all outcomes.

3. Results

Data were collected from 126 eligible patients who received nintedanib across 8 UK ILD centres (Figure 1, Supplementary Table 1). There were 67/126 females (53%), mean age was 60 (±13) years (Table 1). At initiation of nintedanib, mean FVC was 1.86L (± 0.70L; 57.62% ± 18.56%) and mean ppDLco was 32.66% (±11.04%). 5 patients who were approved for nintedanib declined to commence therapy.

The most frequent diagnoses were fHP (n=44/126; 35%) and CTD-ILD (n=44/126; 35%). For the purposes of the secondary analyses, the remainder of patients were categorised as "other" diagnoses and these included unclassifiable IIP (n=9/126; 7%), fibrotic non-specific interstitial pneumonia (NSIP) (n=8/126; 6%) and fibrotic organising pneumonia (OP) (n=4/126; 3%) (Table 1). The CTD-ILD group comprised 24 patients with systemic sclerosis-associated ILD (SSc-ILD), 7 patients with rheumatoid arthritis-associated ILD (RA-ILD) and 13 patients with other connective tissue diseases.

The radiological pattern of fibrosis was definite UIP in 30/126 (24%) patients. Amongst those with non-UIP, the CT was most commonly reported as fHP (n=35) and fibrotic NSIP (n=33).

At the time of nintedanib initiation the most prescribed immunosuppressive drugs were prednisolone and mycophenolate mofetil (MMF) in 86/126 (68%) and 70/126 (56%) patients respectively. The median dose of prednisolone was 10mg (IQR 9-10) and the median dose of MMF was 2g (IQR 1.5-

2g) per day. In total 87/126 (69%) of patients were prescribed a steroid sparing agent and 79/126 (63%) patients were prescribed oxygen. At the time of data collection, 44/126 (35%) patients had been or were currently being assessed for lung transplantation. Six patients were active on the lung transplant list, an additional 19 patients were undergoing assessment and 19 patients had previously been assessed and declined for transplantation.

3.1 Primary lung function analysis

In 123 people with lung function available, it was obtained a median of 346.5 days (IQR 281 to 429) prior to initiation, at nintedanib initiation, and 340 days (IQR 267 to 396) post-initiation. Incorporating all lung function time point data available, mean FVC was 2.10L (95%CI 1.97-2.22) pre-initiation, 1.86L (95%CI 1.73-2.00) at drug initiation and 1.77L (95%CI 1.63-1.90) post-initiation. The mean ppDLco was 38.8% (95%CI 36.4-41.2) pre-initiation, 32.7% (95%CI 28.9-35.4) at initiation of nintedanib and 32.4% (95%CI 29.5-35.4) post-initiation.

In 123 people with an FVC recorded, mean FVC change was -239.9ml (95%CI -292.7 to -187.0) in the year (±6 months) pre-initiation and -88.8ml (95%CI -156.2 to -21.3) in the year (±6 months) post-initiation with a significant attenuation of 151.2ml (95%CI 47.5 to 255.0, p=0.004) (Figure 2A, Supplementary Table 2).

In 114 people with ppDLco recorded, mean ppDLco change was -6.1% (95%CI -7.4 to -4.8) pre-initiation and -2.1% post-initiation (95%CI -4.1 to -0.2%), with significant attenuation between rates of 3.93% (95%CI 1.3 to 6.6, p=0.004) (Fig 2B, Supplementary Table 2). In 108 people with ppKCO recorded, there was a mean ppKco change of -5.7% (95%CI -8.4 to -3.0) pre-initiation with a post-initiation change of -1.3% (95%CI -5.2 to +2.7) and a non-significant reduction in rate of change of 4.43% (95%CI -1.0 to 9.9; p=0.109) (Figure 2C, Supplementary Table 2).

Results of the sensitivity analyses were similar to the overall analysis (Supplementary Table 3, Supplementary Figure 1). Patients experienced a mean ppFVC change of -6.6%/year (95%CI -8.5 to -4.8) pre-initiation and -3.0%/year (95%CI -5.2 to -0.7) post-initiation, with an attenuation of 3.7%/year (95%CI 0.3 to 7.0, p=0.032). Sixty four patients (64/126; 51%) had complete lung function at all three time points, patients with incomplete lung function (n=62/126) were older (mean age 62.7 v 57.8 years, p=0.034) and had more severe MRC dyspnoea scores (p=0.002), but there was no difference in gender, baseline FVC or ppDLco, diagnosis or CT pattern. Strategies for handling missing lung function suggested a similar attenuation of decline post-nintedanib.

3.2 Secondary lung function analyses

Regardless of diagnosis, patients experienced a similar reduced rate of decline in FVC with nintedanib, however statistical significance was not reached (Figure 3, Supplementary Table 2). The difference between the 12-month post-nintedanib and pre-nintedanib rate of FVC change was +125.4ml/yr (95%CI -18.4 to +269.1, p=0.087) in patients with fHP, +122.5ml/yr (95%CI -47.7 to +292.7, p=0.158) in patients with CTD-ILD and +172.7ml/yr (95%CI -25.8 to +371.2 p=0.088) for the 'other' diagnosis group. A significant attenuation in the rate of ppDLco change was observed in individuals with fHP (+5.0%/yr, 95%CI+1.1 to +8.9; p=0.013) and the 'other' diagnosis grouping (+6.6%/yr, 95%CI +1.9 to +11.4; p=0.006), but not in those with CTD-ILD (+0.6%/yr, 95%CI -3.9 to +5.1; p=0.803). No significant difference in ppKco change was observed across diagnoses.

There was a reduced rate of FVC and ppDLco decline in those with a non-UIP pattern and similar in UIP although this did not reach significance (Figure 4, Supplementary Table 2). There was a significant FVC decline in males but not females, whilst a significant ppDLco decline in females but not males, estimates were in the same direction for both sexes (Supplementary Figure 2, Supplementary Table 2).

All secondary subgroup analyses were comparable in restricted analysis of the difference in delta FVC across subgroups (Supplementary Figure 3).

3.3 Symptoms, safety and tolerability

Patient symptoms

Of those surviving to follow-up (n=108/126), the proportion of patients who reported an improvement in symptoms increased after nintedanib treatment. Improvements in shortness of breath were reported in 25.9% (28/108) of people after 12 months of nintedanib compared to 12.0% (13/108) in the 12 months prior to drug initiation (relative difference 15.8%, 95% CI 7.5 to 24.0, p=0.0007). Reported exercise tolerance was similarly improved in 29.6% (32/108) after nintedanib compared to 13.0% (14/108) at initiation (relative difference 19.1%, 95%CI 10.0 to 28.3, p=0.0003). No change was observed in reported cough symptoms (relative difference 3.0%, 95%CI -11.1 to 17.1, p=0.839).

Drug side effects and tolerability

Across the entire cohort (n=126), at least one side effect was experienced by 89/126 (71%) patients (Table 2). Diarrhoea was the most common side effect (n=49/126; 39%). Hepatotoxicity was reported in 8/126 (6%) patients and was not more commonly reported in patients on steroid sparing agents (p=0.702). No serious adverse events associated with nintedanib treatment were recorded. Eighteen patients (18/126; 14%) died during the study period, for which complications or progression of ILD accounted for 8/18.

The dose of nintedanib was reduced in 37/126 (29%) patients, most commonly due to diarrhoea (n=23/37; 62%). Patients whose nintedanib dose was reduced experienced a similar benefit in lung function stabilisation (Supplementary Figure 4, Supplementary Table 4). Fifty patients (50/126; 40%) underwent a change in immunosuppressive treatment in the year following nintedanib initiation, but this was not associated with a difference in rate of lung function change (Supplementary Table 5).

Drug discontinuation

Nintedanib was discontinued before 1 year of treatment in 40/126 (32%) patients due to death (n=18),side effects (n=21), or other reasons (n=1). Patients who stopped nintedanib before 12 months of treatment were non-statistically older (mean difference 4.9 years; 95%CI -0.02 to 9.87, p=0.051). No difference was observed in FVC or DLco at treatment initiation in those who discontinued nintedanib but these patients had a lower Kco (mean difference -11.70%; 95%CI -21.28 to -2.12, p=0.017). Patients with higher MRC scores were less likely to continue treatment for 12 months; 19 of the 29 patients (66%) who survived but stopped treatment before 12 months had an MRC score of 4 or 5 at drug initiation compared to 24/62 patients (39%) who continued treatment to 12 months (p=0.027).

4. Discussion

This study has demonstrated that for patients with non-IPF PPF in a real-world setting, the decline of lung function is significantly attenuated following the introduction of nintedanib. Although it is challenging to directly compare real world data with that acquired from highly protocolised clinical trials, patients experienced a mean FVC decline of -240 ml in the 12 months prior to nintedanib treatment as compared with -89 ml in the 12 months after treatment initiation (difference of 151 ml per year) mirroring the results of the INBUILD trial (FVC decline of -187ml per year with placebo vs -80ml per year with nintedanib)(12). Furthermore, there was also parallel attenuation in ppDLco decline associated with nintedanib, an effect which has historically been challenging to observe in multi-centre clinical trials due to inter-laboratory variability. The early access nature of this study meant that the patients had more advanced disease at drug initiation compared to those recruited to INBUILD (mean FVC 1.86L vs 2.34L and DLco 32.7% vs 44.4% respectively). Despite this, the observation that nintedanib is effective in slowing the rate of lung function decline is highly reassuring. Previous real-world studies have shown that nintedanib slows the progression of IPF (18-20), however this is the first real-world study assessing its efficacy in non-IPF PPF.

The attenuating effect was observed across diagnostic sub-groups, HRCT patterns and sex to similar extents. Nintedanib was safe and well tolerated when prescribed alongside a broad range of immunosuppressive regimes, some of which were restricted in previous clinical trials. This supports data from subgroup analyses data of the SENSCIS study showing no adverse interaction between

nintedanib and mycophenolate mofetil(21). Most patients were prescribed corticosteroids and at least one steroid sparing agent with infrequent reports of hepatoxicity or debilitating gastrointestinal side effects. Although 71% of patients reported at least one side effect, most commonly diarrhoea, 80% of surviving patients were still taking nintedanib at 12 months. Dose reductions were required in 29% of patients but did not appear to reduce the efficacy of nintedanib. 17% of patients discontinued nintedanib before 12 months due to side effects; these patients had greater baseline dyspnoea and a lower ppKco that may reflect additional comorbidity.

In this prevalent PPF population with severe disease at initiation, nintedanib was potentially associated with a reduced perception of symptomatic decline with a greater proportion of patients reporting improvements in shortness of breath and exercise tolerance following nintedanib initiation than before treatment. This finding is hypothesis generating and may be explained by the placebo effect of a new therapy or indeed concomitant introduction of palliative treatments. Although data regarding pulmonary rehabilitation were not available, the study period coincided with the height of the COVID pandemic when services were highly restricted making it less likely that widespread uptake of rehabilitation could explain these results. These observations have implications for patient selection as advanced age, frailty and disease severity should not necessarily preclude antifibrotic treatment. The lack of patient reported impact on cough does however highlight an unmet need.

4.1 Strengths and Limitations

Eight specialist ILD centres contributed to the study with only 10/126 (8%) of patients not meeting newly published official ATS/ERS/JRS/ALAT Clinical Practice Guideline for patients with PPF(3), supporting the generalisability of the results. The breakdown of ILD diagnoses in this study paralleled INBUILD; the most common diagnoses were fHP and CTD-ILD (12, 14). There were more patients with SSc-ILD (24%) than in INBUILD (<7%)(12) but the proportion was similar to the PROGRESS study(6) and thus may be a more accurate reflection of the real-world population. The INBUILD cohort had a higher proportion of UIP scans incorporating both definite and probable UIP(3) whereas in our study only definite UIP was classified as such. Almost all patients who were eligible received treatment with only a small number (n=5) electing not to start nintedanib – this means that selection bias is unlikely to have skewed the results.

As this was a real-world study of patients treated with nintedanib through an early access programme, data was acquired through routine clinical care as opposed to a protocolised clinical study, which resulted in missing data, particularly of lung function records. Study recruitment and follow-up was conducted between May 2019 and August 2021, therefore the Covid-19 pandemic further compounded the issue as recommended shielding guidance and repositioning of health resource impacted lung function visits, hospitalisations and acute exacerbations. Comparisons drawn between lung function decline pre- and post-treatment exposure may therefore be limited by the time and

progression course. Patients not providing lung function data at the final time point could over-estimate the benefit of the drug due to survivorship bias.

To ensure that all patients entered onto the early access programme were represented in primary analyses, multilevel models for repeat measures were used. Sensitivity analysis restricted solely to those patients who provided lung function data at three timepoints demonstrated a similar magnitude of effect with nintedanib. Routine clinical lung function is frequently missing not at random due to the effort required in severe disease. Further sensitivity analyses were performed with alternative single imputation strategies for data missing not at random,(22) and continued to support an attenuation in lung function decline.

The secondary analysis was limited by small numbers in subgroups, restricting power to detect between group differences including potential confounding effects of immunosuppression. Patient reported symptom scores were subjectively evaluated from clinic letters and not prospectively assessed using validated questionnaires. Whilst intolerable side effects due to nintedanib were not reported, improvement in symptoms are subject to bias and require independent validation. UIP and non-UIP HRCT patterns were reported by ILD teams based on radiology reports and not centrally evaluated, however all centres are specialist ILD units and local interpretation is considered acceptable for many drug clinical trials.

4.2 Conclusion

In this first, antifibrotic treated, real-world multicentre study of patients with non-IPF PPF patients, we have demonstrated that nintedanib was safe, well tolerated, and associated with an attenuation of lung function decline despite the severity of ILD in this patient cohort. Nintedanib did not appear to have excess deleterious effects when taken in combination with other immunosuppressants, supporting its use for the pharmacological treatment of non-IPF ILD where progression has occurred despite optimal management.

Author contributions:

PMG conceived the study, coordinated data collection, analysed the data and drafted the manuscript. LR coordinated data collection, analysed the data and wrote the first draft of the manuscript. IS provided statistical oversight, analysed the data and drafted the manuscript. PMG, LR and IS had direct access to the data. All authors were involved in data collection, critical appraisal and approved the final version of the manuscript.

Role of the funder:

This study was not externally funded

Conflicts of interest:

IS receives funding from the Rayne Foundation. NC reports personal fees from Boehringer Ingelheim, Redex, Novartis, Liminal Biosciences, Vicor Pharma, Bridge Biotherapeutics and Roche. FC reports personal fees from Boehringer Ingelheim. CH has received personal fees from Boehringer Ingelheim. MG reports personal fees for advisory boards and support for attending conferences from Boehringer Ingelheim. VK reports personal fees from Boehringer Ingelheim and Novartis. SM reports personal fees from Boehringer Ingelheim. MN reports honoraria from Boehringer Ingelheim, Astra Zeneca and Roche and grant support paid to their institution from an NHSX digital award. EAR reports fees paid to their institution from Boehringer Ingelheim, Novartis Roche and research grants paid to their institution from Boehringer Ingelheim. MT reports personal fees from Boehringer Ingelheim, research grants paid to their institution from Boehringer Ingelheim and support for conference attendance from Boehringer Ingelheim. AUW is president elect of WASOG, reports personal fees from Boehringer Ingelheim and Roche and support for conference from Boehringer Ingelheim. PMG reports personal fees from Boehringer Ingelhein, Roche, Teva, Cipla and Brainomix, research grants paid to their institution from Boehringer Ingleheim and support for conference attendance from Boehringer Ingelheim and Roche. No other authors report any conflicts of interest.

Table 1. Baseline characteristics and lung function at initiation of nintedanib

	N 126	Mean	SD
Age (years)	126	60	13
Baseline lung function			
FVC (L)	103	1.86	0.70
FVC (% predicted)	102	57.62	18.56
DLco (% predicted)	79	32.66	11.04
Kco (% predicted)	74	65.85	18.97
	Category	**N**	**Percentage**
Gender			
	Male	59	47
	Female	67	53
ILD diagnosis			
	fHP	44	34.9
	CTD-ILD	44	34.9
	Unclassifiable IIP	9	7.1
	Fibrotic NSIP	8	6.3
	Fibrotic OP	4	3.2
	PPFE	3	2.4
	Asbestosis	3	2.4

	Smoking related ILD	3	2.4
	Familial PF	1	0.8
	Fibrotic sarcoid	1	0.8
	DIP	1	0.8
	HIV associated ILD	1	0.8
	Other	4	3.2
Smoking status			
	Current	2	1.6
	Ex	46	36.5
	Never	63	50
	No data	15	11.9
Hospital			
	Guy's & St Thomas' NHS Foundation trust	10	7.9
	Manchester University NHS Foundation Trust	13	10.3
	North Bristol NHS Trust	3	2.4
	Oxford University Hospital	16	12.7
	Royal Papworth Hospital	15	11.9
	Royal Brompton Hospital	61	48.4
	Royal Devon & Exeter Hospital	4	3.2
	University Hospital Birmingham	4	3.2
MRC Dyspnoea score			
	1	4	3
	2	18	14
	3	26	21
	4	27	21
	5	16	13
	No data	35	28
Home Oxygen (ambulatory/LTOT)			
	Yes	79	62.7
	No	45	35.7
	Unknown	2	1.6
Fibrotic pattern on CT			
	UIP	30	24
	Non-UIP	95	75
	No Data	1	1
Indication for starting Nintedanib			
	Progressive symptoms	111	88
	Lung function decline	100	79
	CT progression	85	67
Concurrent Immunosuppression			
	Yes	113	90
	No	13	10
	Prednisolone	86	68
	Mycophenolate mofetil	70	56

	Azathioprine	6	5
	Hydroxychloroquine	13	10
	Leflunomide	3	2
	Rituximab	9	7
	Tacrolimus	1	1
	Methotrexate	3	2
Change in immunosuppression following nintedanib initiation			
	Unchanged	76	60
	Increased	29	23
	Decreased	13	10
	Other	8	6

Table 1 Legend. FVC denotes forced vital capacity; DLco: diffusion capacity of the lung for carbon monoxide; Kco: carbon monoxide transfer coefficient; fHP: fibrotic hypersensitivity pneumonitis; CTD-ILD: connective tissue disease-associated interstitial lung disease; unclassifiable IIP: unclassifiable idiopathic interstitial pneumonia; fibrotic NSIP: fibrotic non-specific interstitial pneumonia; fibrotic OP: fibrotic organising pneumonia; PPFE: pleuroparenchymal fibroelastosis; familial PF: familial pulmonary fibrosis; DIP: desquamative interstitial pneumonia; HIV: human immunodefiency virus; LTOT: long-term oxygen therapy; UIP: usual interstitial pneumonia

Table 2. Tolerability, safety and survival related to nintedanib

		N 126	Percentage
Adverse effects			
	Yes	89	71
	Diarrhoea	49	39
	Nausea & vomiting	31	25
	Weight loss	31	25
	Abdominal pain	22	17
	Appetite loss	11	9
	Hepatotoxicity	8	6
	Headache	8	6
	Constipation	3	2
	Lethargy	3	2
	Other	2	2
	None	37	29
Dose reduction nintedanib?			
	Yes	37	29
Surviving patients who completed at least 6 months of nintedanib			
	Yes	102	81
	No	24	19
Surviving patients on nintedanib at 12 months			
	Yes	86	80
	No	22	20
Survival at 12 months			
	Alive	108	86
	Dead	18	14

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Figure Legends

Figure 1. CONSORT flow diagram of study population

Study CONSORT demonstrating the number of eligible participants, those initiated on nintedanib, those reaching primary analysis criteria of sequential lung function, adherence to the compassionate access programme.

Figure 2. Difference in lung function change in the 12 months pre- and post-nintedanib initiation (N=123)

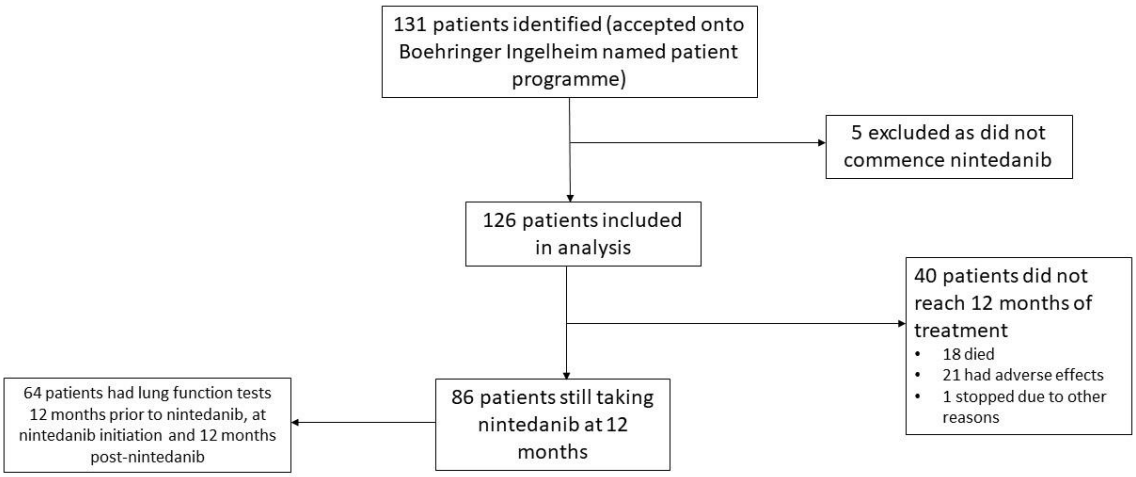
Mean lung function (A) FVC (ml; n=123), (B) ppDLco (% predicted; n=114) and (C) ppKco (% predicted; n=108) values at pre-initiation, initiation and post-initiation, and the difference in rate of lung function change pre and post initiation. Estimates plotted with 95% confidence intervals from multilevel model.

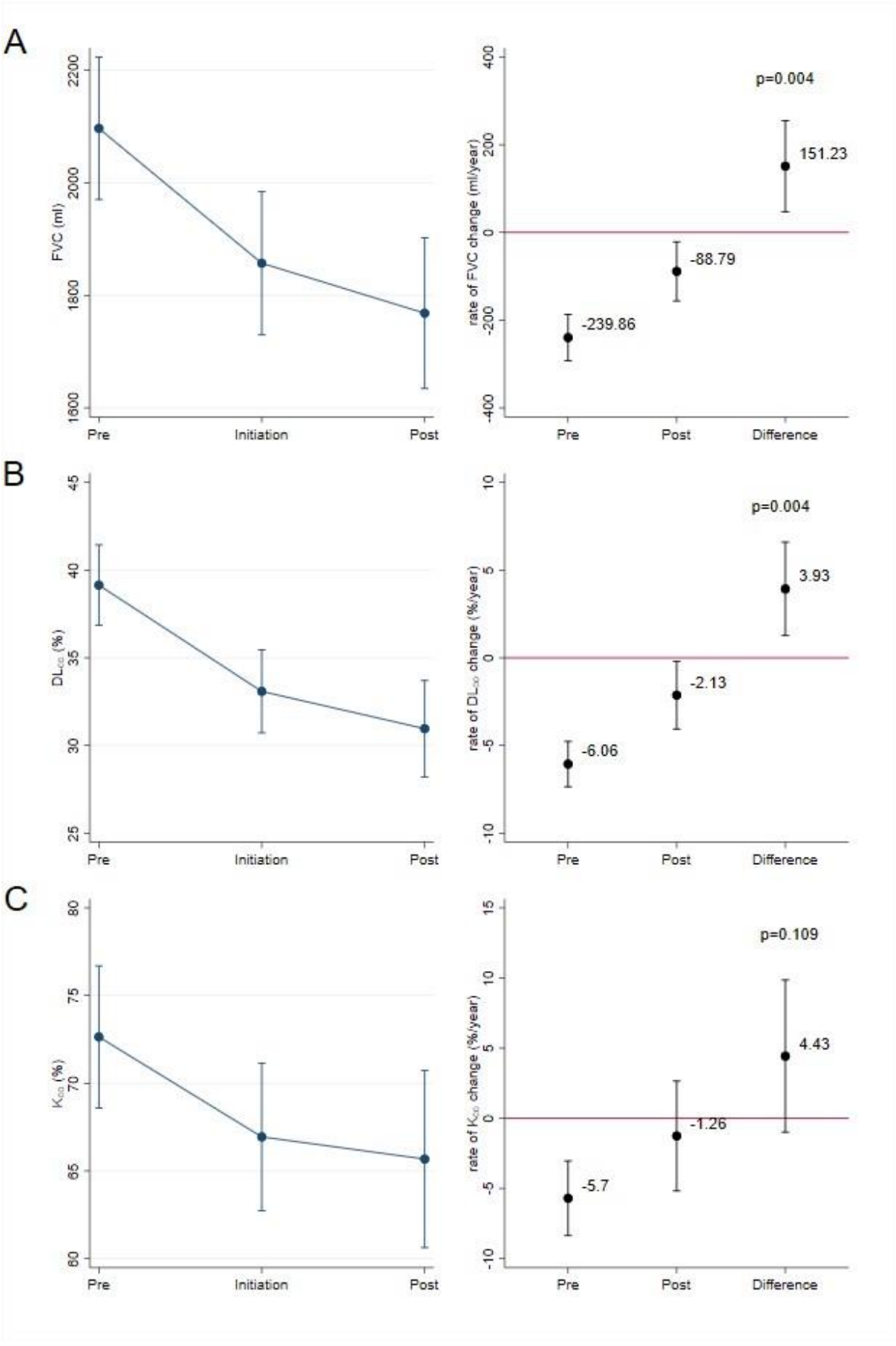
Figure 3. Difference in lung function change between 12 months pre and post nintedanib according to diagnostic group (N=123)

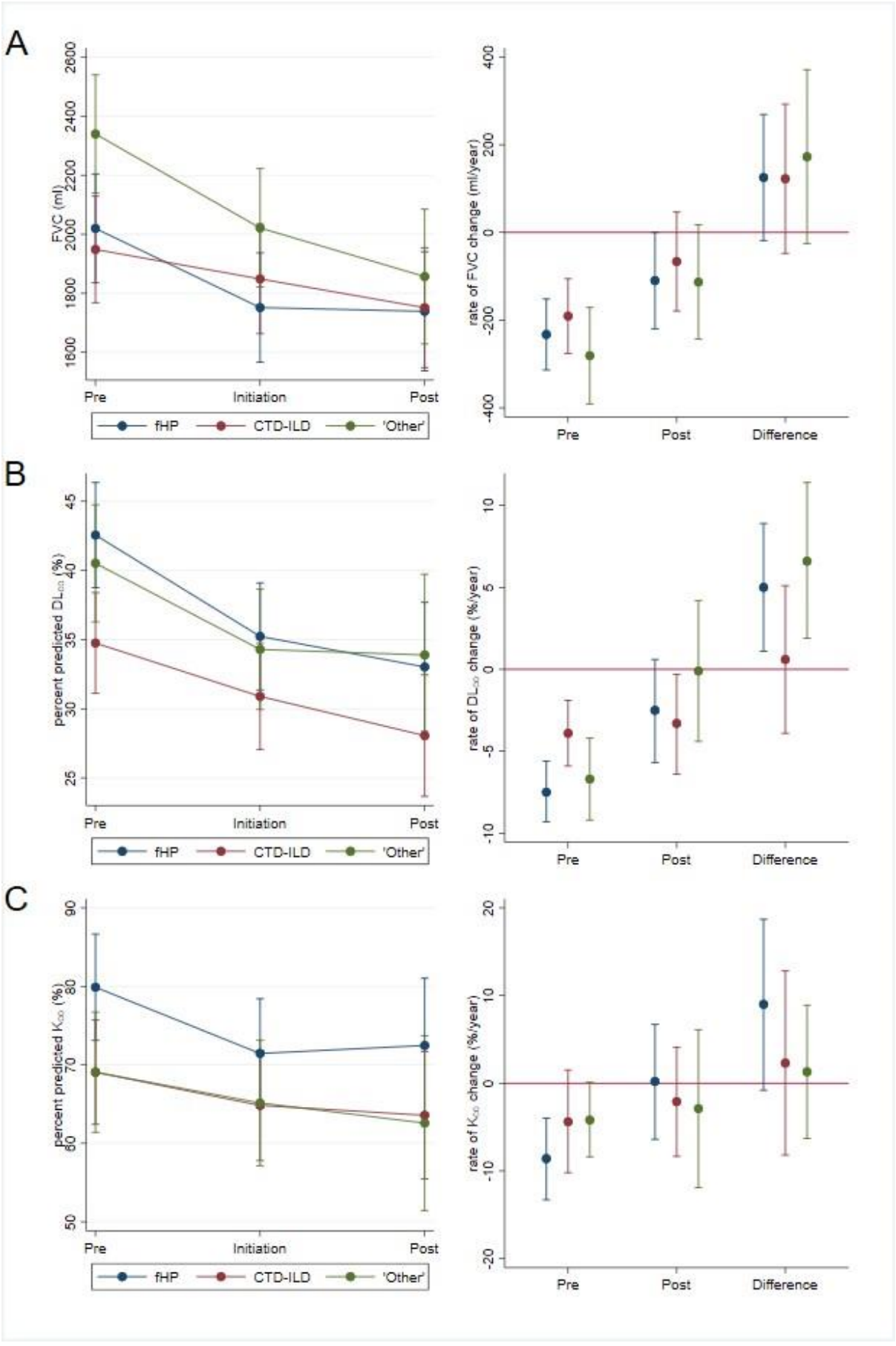
Adjusted estimates of mean lung function (A) FVC (ml; n=123), (B) ppDLco (% predicted; n=113) and (C) ppKco (% predicted; n=107) values at pre-initiation, initiation and post-initiation, and the difference in rate of lung function change pre and post initiation, according to diagnostic group. Estimates plotted with 95% confidence intervals. fHP – fibrotic hypersensitivity pneumonitis; CTD-ILD – connective tissue disease-associated ILD.

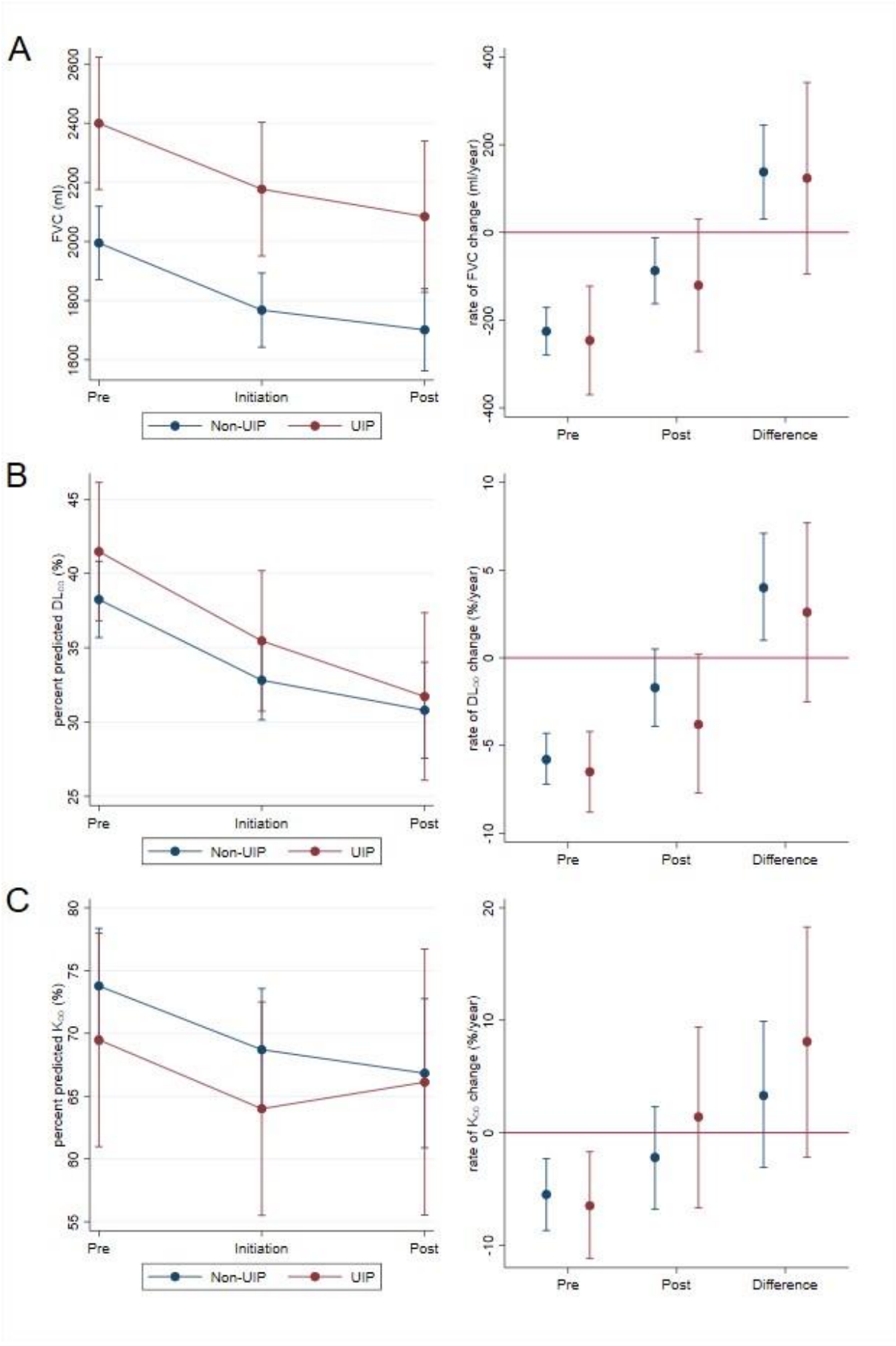
Figure 4. Difference in lung function change between 12 months pre and post nintedanib according to CT pattern (N=123)

Adjusted estimates of mean lung function (A) FVC (ml; n=123), (B) ppDLco (% predicted; n=113) and (C) ppKco (% predicted; n=107) values at pre-initiation, initiation and post-initiation, and the difference in rate of lung function change pre and post initiation, according to CT pattern. Estimates plotted with 95% confidence intervals.


131 patients identified (accepted onto Boehringer Ingelheim named patient programme)
5 excluded as did not commence nintedanib
126 patients included in analysis
40 patients did not reach 12 months of treatment
• 18 died
• 21 had adverse effects
• 1 stopped due to other reasons
86 patients still taking nintedanib at 12 months
64 patients had lung function tests 12 months prior to nintedanib, at nintedanib initiation and 12 months post-nintedanib


A
FVC (ml)
2200
2000
1800
1600
Pre
Initiation
Post
rate of FVC change (ml/year)
400
200
0
-200
-400
p=0.004
151.23
-88.79
-239.86
Pre
Post
Difference
B
DLCO (%)
45
40
35
30
25
Pre
Initiation
Post
rate of DLCO change (%/year)
10
5
0
-5
-10
p=0.004
3.93
-2.13
-6.06
Pre
Post
Difference
C
KCO (%)
80
75
70
65
60
Pre
Initiation
Post
rate of KCO change (%/year)
15
10
5
0
-5
-10
p=0.109
4.43
-1.26
-5.7
Pre
Post
Difference


A
FVC (ml)
1600
1800
2000
2200
2400
2600
Pre
Initiation
Post
fHP
CTD-ILD
'Other'
rate of FVC change (ml/year)
-400
-200
0
200
400
Pre
Post
Difference
B
percent predicted DLco (%)
25
30
35
40
45
Pre
Initiation
Post
fHP
CTD-ILD
'Other'
rate of DLco change (%/year)
-10
-5
0
5
10
Pre
Post
Difference
C
percent predicted Kco (%)
50
60
70
80
90
Pre
Initiation
Post
fHP
CTD-ILD
'Other'
rate of Kco change (%/year)
-20
-10
0
10
20
Pre
Post
Difference


A
FVC (ml)
1800
2000
2200
2400
2600
Pre
Initiation
Post
Non-UIP
UIP
rate of FVC change (ml/year)
-400
-200
0
200
400
Pre
Post
Difference
B
percent predicted DLco (%)
25
30
35
40
45
Pre
Initiation
Post
Non-UIP
UIP
rate of DLco change (%/year)
-10
-5
0
5
10
Pre
Post
Difference
C
percent predicted Kco (%)
55
60
65
70
75
80
Pre
Initiation
Post
Non-UIP
UIP
rate of Kco change (%/year)
-10
0
10
20
Pre
Post
Difference

A National study of Nintedanib for Progressive Fibrosing Interstitial Lung Disease

1. AUDIT LOCATION

Name of Hospital……

2. PATIENT DETAILS AND DEMOGRAPHICS

Local ID/MRN (e.g. RBH 001)……

Patient Initials……

Audit Number (to be assigned by RBH)……...

Age at initiation of nintedanib (years)					
Sex	M ☐	F ☐			
Ethnicity	White ☐	Black ☐	Asian ☐	Mixed ☐	Other ☐
Smoking	Current ☐	Ex ☐	Never ☐		
Height (m)					
BMI (kg/m2)					
Known to hospital or community palliative care services	Yes ☐		No ☐	Not Sure ☐	

3. DIAGNOSES

ILD diagnosis:

Chronic Hypersensitivity Pneumonitis	Yes ☐	No ☐			
Autoimmune ILD	Yes ☐	No ☐	If yes please specify		Tick
				Rheumatoid related ILD	☐
				Systemic sclerosis-associated ILD	☐
				Mixed connective tissue disease-associated ILD	☐
				Other autoimmune ILD	☐
Unclassifiable idiopathic interstitial pneumonia	Yes ☐	No ☐			
Idiopathic non-specific interstitial pneumonia	Yes ☐	No ☐			
Other	Yes ☐	No ☐	Please Specify		

Comorbidities

……
……
……
……
……
……
……

Medication

Medication (please include Nintedanib and dose)	Dose	Date commenced (Please only complete for immunosuppressive therapy; leave blank if unknown)

Immunomodulators (including steroids)

Was a new immunomodulator commenced after Nintedanib initiation?	Yes ☐		No ☐	Unknown ☐
	Drug(s)	Indication for starting		
Were any immunomodulators discontinued after Nintedanib initiation?	Yes ☐		No ☐	Unknown ☐
	Drug(s)	Indication for stopping		
Was the dose of immunomodulator changed after Nintedanib initiation?	Yes ☐		No ☐	Unknown ☐
	Drug(s)	Indication for change		

Severity of disease

MRC dyspnoea grade (1-5)				Not Known ☐
Home Oxygen	Yes ☐		No ☐	Not Known ☐
	Ambulatory ☐	LTOT ☐		
	Commenced prior to Nintedanib initiation ☐	Commenced after Nintedanib initiation ☐		
Was the patient ever referred for transplant?	Yes ☐	Declined ☐	No ☐	Not Known ☐
		Under assessment ☐		
		On active transplant waiting list ☐		

Family history

Does the patient have a familial history of ILD?	Yes ☐	No ☐	Unknown ☐	**IF YES** Specify type of ILD			
				First Degree Relatives		Second Degree Relatives	
				Yes ☐	No ☐	Yes ☐	No ☐

4. BASIS FOR ENTRY ONTO THE PROGRAMME – Please send anonymised Nintedanib initiation proforma

Date accepted onto the programme……

Date of initiation of Nintedanib……..

Indication for entry onto programme (select all that apply)	YES	NO	DETAILS
Progressive symptoms	☐	☐	
Progressive fibrosis on CT	☐	☐	
Progressive decline in lung function	☐	☐	
Increasing oxygen requirement	☐	☐	
Other (please specify)	☐	☐	

5. RADIOLOGY- Please attach anonymised reports of all previous CT scans

	Initial CT preceding nintedanib		CT at initiation of nintedanib (leave blank if no CT)		Follow up CT scan post nintedanib initiation (leave blank if no CT)	
Date of CT						
CT report						
Progression of fibrosis from previous CT?	YES ☐	NO ☐	YES ☐	NO ☐	YES ☐	NO ☐
Predominant radiological ILD pattern	Usual interstitial pneumonia (UIP)					☐
	Fibrotic non-specific interstitial pneumonia (NSIP)					☐
	Fibrotic hypersensitivity pneumonitis (HSP)					☐
	Fibrotic organising pneumonia (OP)					☐
	Fibrotic sarcoid					☐
	Other					☐

		(specify)

6. LUNG FUNCTION – Please attach serial formal lung function reports including any tests performed prior to those entered in the table below

	24 months prior to Nintedanib initiation (+/- 6 months)	12 months prior to Nintedanib (+/- 6 months)	At initiation of Nintedanib (+/- 6 months)	12 months after initiation of Nintedanib (+/- 6 months)
Date of lung function				
Weight at time of test				
Height at time of test				
FEV_1 (L)				
FEV_1 (% predicted)				
FVC (L)				
FVC (% predicted)				
TLco				
TLco (% predicted)				
Kco				
Kco (% predicted)				

7. SYMPTOMATIC PROGRESSION

Please rate the patient's symptoms according to the following scale (leave blank if no data):

1: Rapid/severe deterioration

2: Mild/moderate deterioration

3: No change

4: Mild/moderate improvement

5: Significant improvement

	12 months preceding Nintedanib initiation	Since Nintedanib initiation
Dyspnoea	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
Cough	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
Exercise tolerance	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
Other symptom related to ILD (specify)	☐ 1 ☐ 2	☐ 1 ☐ 2

	☐ 3 ☐ 4 ☐ 5	☐ 3 ☐ 4 ☐ 5

Did the patient have a health-related quality of life score (e.g. K-BILD, EQ 5D)?

YES ☐ NO ☐

Name of score			
	12 months prior to Nintedanib (+/- 6 months)	At initiation of Nintedanib (+/- 6 months)	12 months after initiation of Nintedanib (+/- 6 months)
Date of score			
Score			

8. ADVERSE DRUG EVENTS

	YES	NO	Unknown/ not applicable	DETAILS/REASON	
Did the patient experience adverse effects of Nintedanib?	☐	☐	☐	*Specify adverse effects*	
Did the patient develop hepatotoxicity?	☐	☐	☐		
Did the patient develop GI side effects?	☐	☐	☐	*Specify GI effects*	
Did the patient require anti-diarrhoeal medication?	☐	☐	☐		
Was the dose of Nintedanib reduced?	☐	☐	☐	*Reason for change*	
				Dose change 1 (inc frequency)	*Duration on new dose*
				Dose change 2 (inc frequency)	*Duration on new dose*
Did the patient require dose reduction of other immunosuppressive therapy (e.g. MMF) to improve tolerability?	☐	☐	☐	*Specify drug and reason*	
Did the patient experience weight loss	☐	☐	☐	*Specify amount*	
Did the patient experience bleeding	☐	☐	☐	*Specify*	
Did the patient require a change in anticoagulant therapy?	☐	☐	☐	*Drug, change and reason*	
Did the patient experience angina or other evidence of ischaemic heart disease	☐	☐	☐	*Specify*	
Is the patient still on Nintedanib at 12 months	☐	☐	☐	If NO:	
				Reason for discontinuation	
				Duration of treatment (months)	

9. RESPIRATORY HOSPITALISATIONS

	12 months preceding Nintedanib initiation	12 months following Nintedanib initiation
Total number of hospital admissions with respiratory symptoms		
GP attendances with worsening of respiratory symptoms		

COVID-19 data

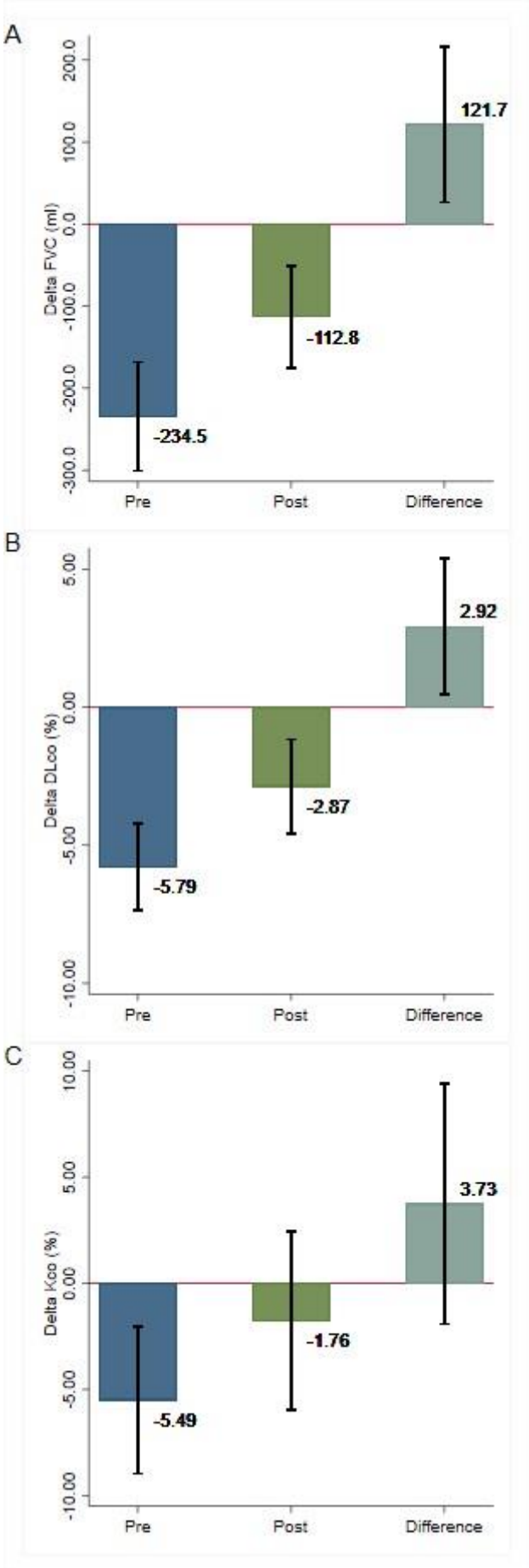
	Yes	No	Unknown	
Was the patient shielding during the national COVID-19 lock down?	☐	☐	☐	
Did the patient suffer from COVID-19 infection?	☐	☐	☐	IF **YES:** Clinical diagnosis ☐ Confirmed diagnosis (PCR) ☐ Confirmed diagnosis (Serology) ☐

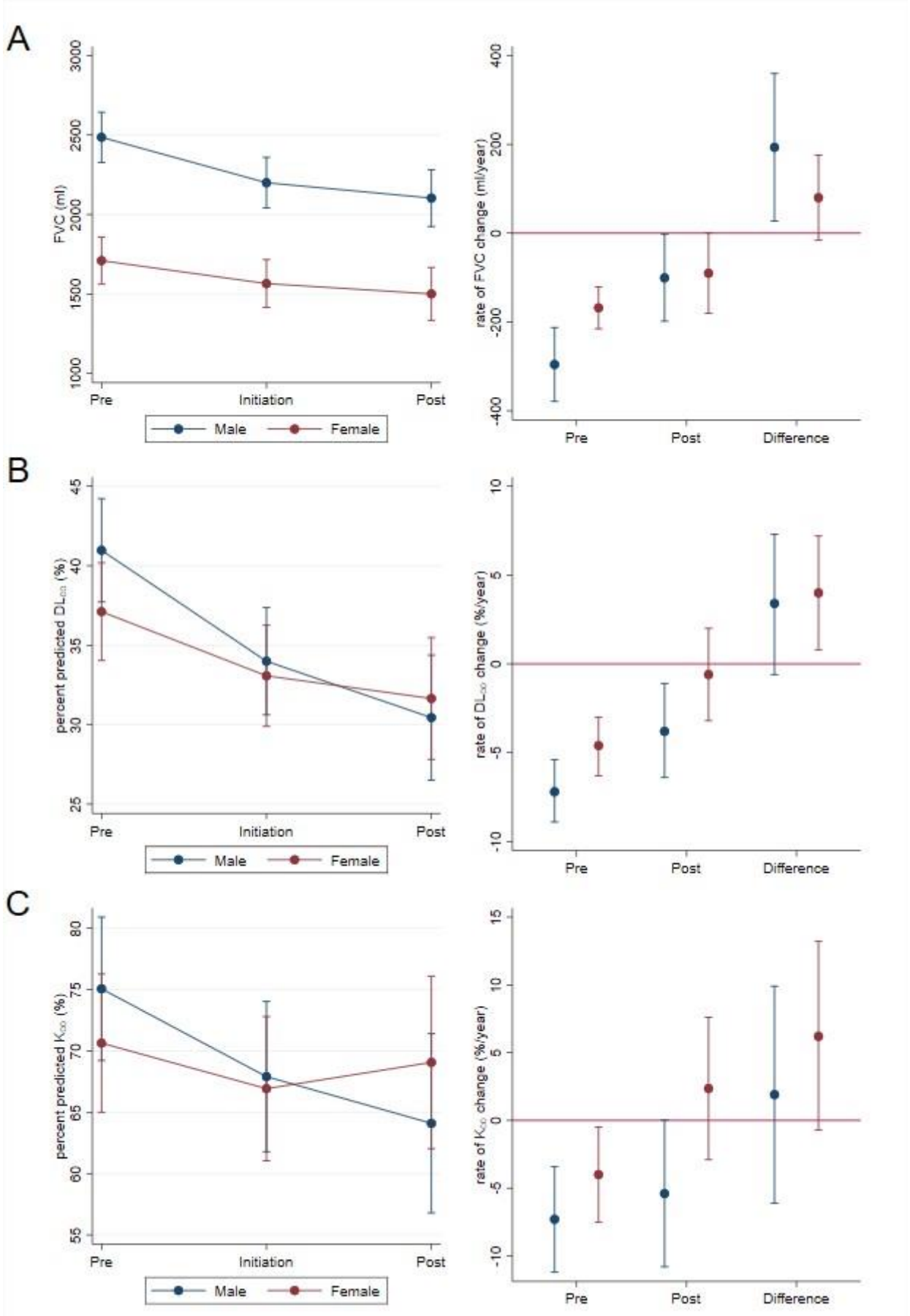
10. ACUTE EXACERBATIONS OF ILD

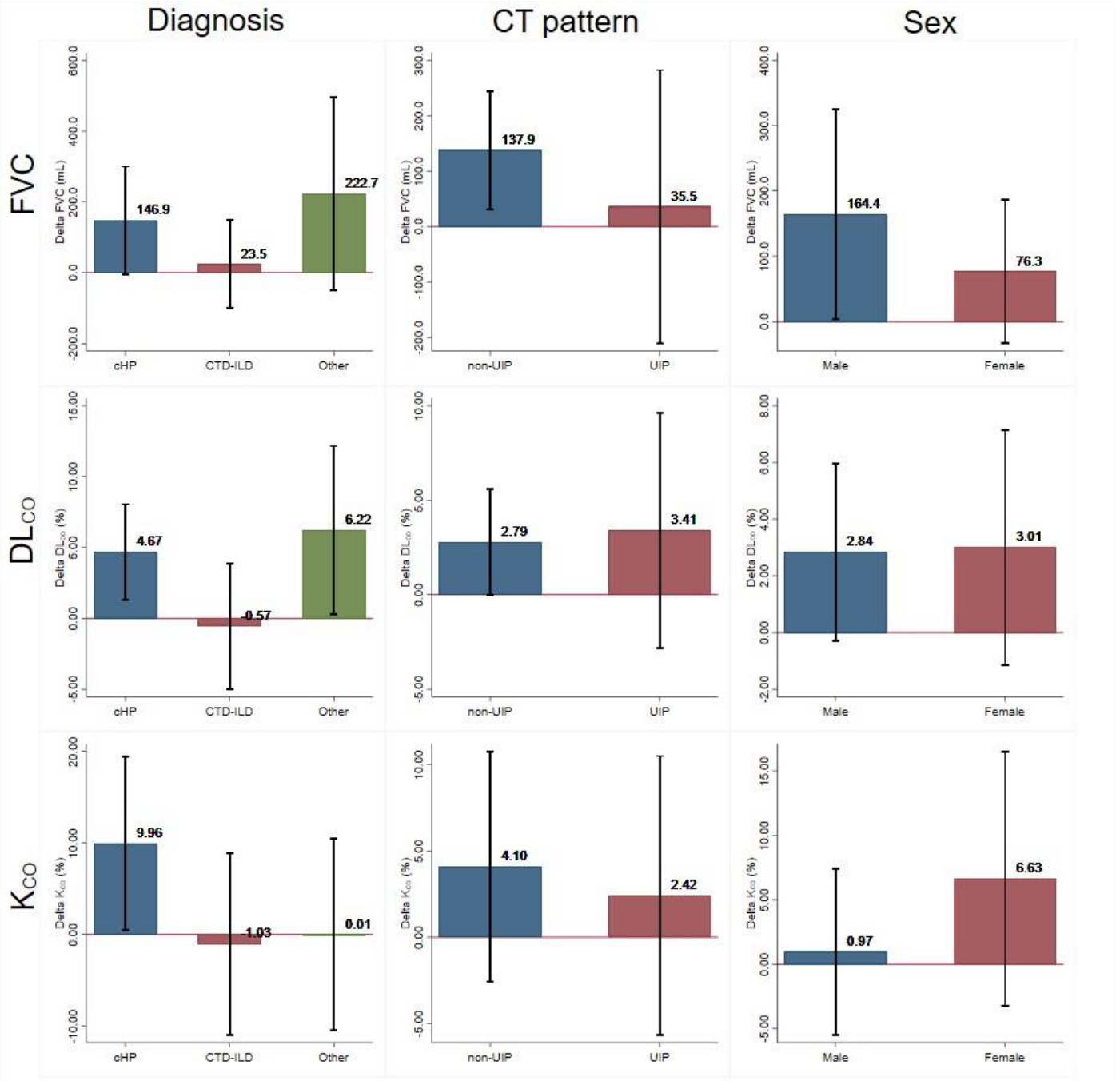
	12 months preceding Nintedanib initiation	12 months following Nintedanib initiation
Total number of hospital admissions with acute exacerbations of ILD		
GP attendances with acute exacerbation of ILD		

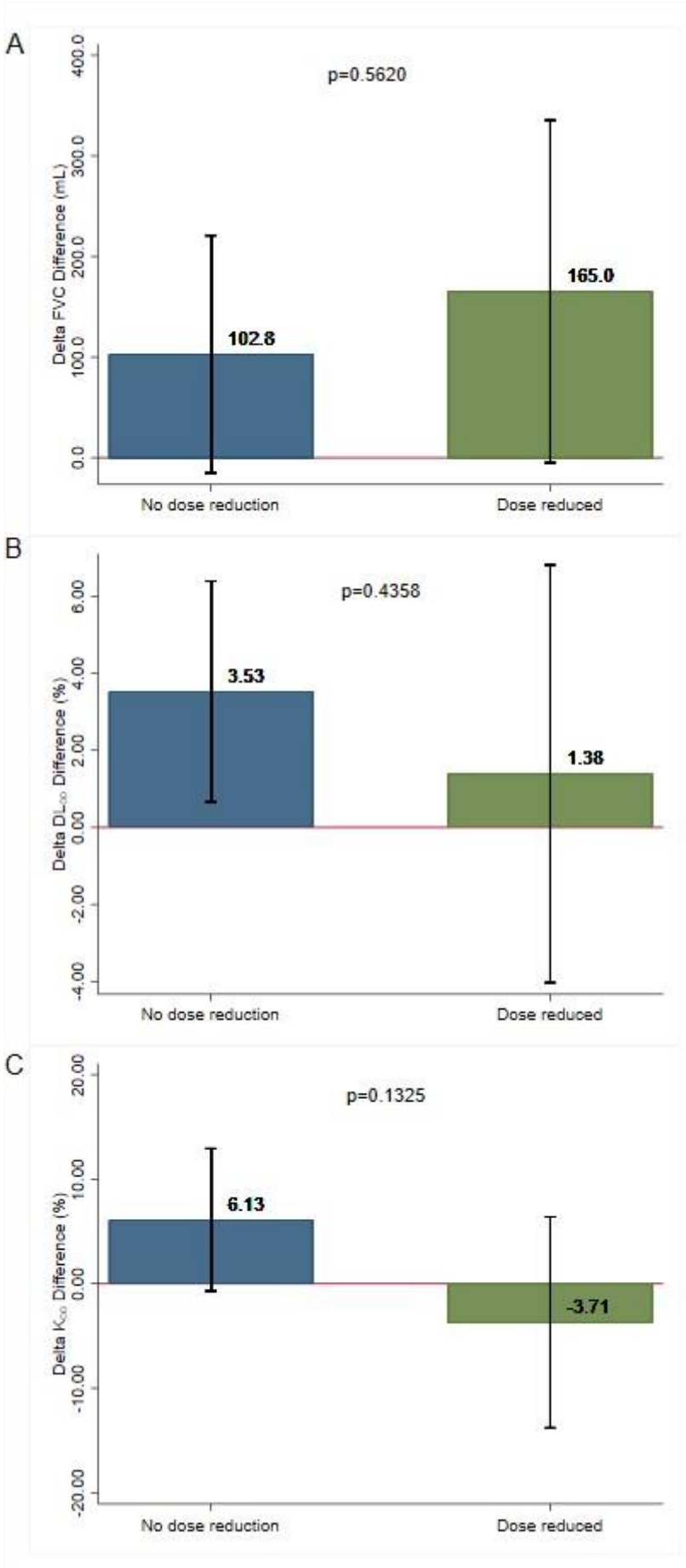
11. SURVIVAL

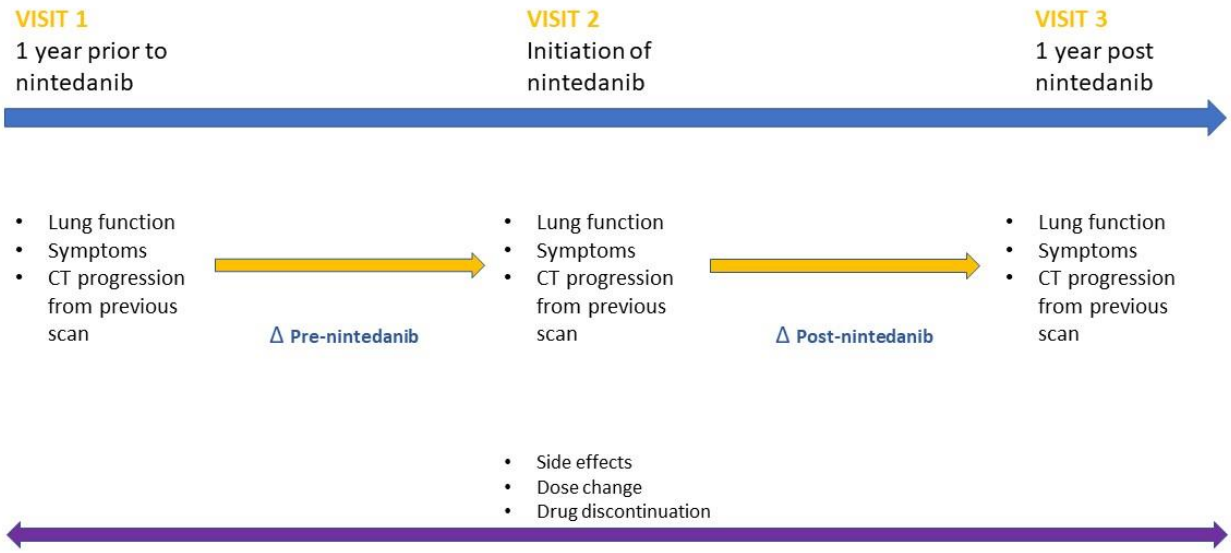
	Yes	No	If **NO**:	
Is the patient alive at 12 months following nintedanib initiation	☐	☐	Cause of death	
			How long after initiation of nintedanib did patient die?	


A
Delta FVC (ml)
200.0
100.0
0.0
-100.0
-200.0
-300.0
121.7
-112.8
-234.5
Pre
Post
Difference
B
Delta DLco (%)
5.00
0.00
-5.00
-10.00
2.92
-2.87
-5.79
Pre
Post
Difference
C
Delta Kco (%)
10.00
5.00
0.00
-5.00
-10.00
3.73
-1.76
-5.49
Pre
Post
Difference


A
FVC (ml)
3000
2500
2000
1500
1000
Pre
Initiation
Post
Male
Female
rate of FVC change (ml/year)
400
200
0
-200
-400
Pre
Post
Difference
B
percent predicted DLco (%)
45
40
35
30
25
Pre
Initiation
Post
Male
Female
rate of DLco change (%/year)
10
5
0
-5
-10
Pre
Post
Difference
C
percent predicted Kco (%)
80
75
70
65
60
55
Pre
Initiation
Post
Male
Female
rate of Kco change (%/year)
15
10
5
0
-5
-10
Pre
Post
Difference


Diagnosis
CT pattern
Sex
FVC
DLCO
KCO
Delta FVC (mL)
Delta DLCO (%)
Delta KCO (%)
146.9
23.5
222.7
137.9
35.5
164.4
76.3
4.67
-0.57
6.22
2.79
3.41
2.84
3.01
9.96
-1.03
0.01
4.10
2.42
0.97
6.63
cHP
CTD-ILD
Other
non-UIP
UIP
Male
Female


A
p=0.5620
Delta FVC Difference (mL)
400.0
300.0
200.0
100.0
0.0
102.8
165.0
No dose reduction
Dose reduced
B
p=0.4358
Delta DL$_{CO}$ Difference (%)
6.00
4.00
2.00
0.00
-2.00
-4.00
3.53
1.38
No dose reduction
Dose reduced
C
p=0.1325
Delta K$_{CO}$ Difference (%)
20.00
10.00
0.00
-10.00
-20.00
6.13
-3.71
No dose reduction
Dose reduced


VISIT 1
1 year prior to nintedanib
VISIT 2
Initiation of nintedanib
VISIT 3
1 year post nintedanib
• Lung function
• Symptoms
• CT progression from previous scan
Δ Pre-nintedanib
• Lung function
• Symptoms
• CT progression from previous scan
Δ Post-nintedanib
• Lung function
• Symptoms
• CT progression from previous scan
• Side effects
• Dose change
• Drug discontinuation

Supplementary information: Nintedanib for non-IPF progressive pulmonary fibrosis: 12-month outcome data from a real-world multicentre observational study

Supplementary Table 1: Complete clinical data

	Time point	N=126	%
FVC			
	Pre-nintedanib	113	89.7%
	Treatment initiation	103	81.7%
	Post-nintedanib	84	66.7%
ppFVC			
	Pre-nintedanib	112	88.9%
	Treatment initiation	102	81.0%
	Post-nintedanib	85	67.5%
ppDLCO			
	Pre-nintedanib	104	82.5%
	Treatment initiation	79	62.7%
	Post-nintedanib	68	54.0%
ppKCO			
	Pre-nintedanib	95	75.4%
	Treatment initiation	74	58.7%
	Post-nintedanib	65	51.6%
Shortness of breath			
	Treatment initiation	113	89.7%
	Post-nintedanib	103	81.7%
Cough			
	Treatment initiation	78	61.9%
	Post-nintedanib	78	61.9%
Exercise tolerance			
	Treatment initiation	112	88.9%
	Post-nintedanib	101	80.2%

Complete data available for each of the above fields at the various points

Supplementary Table 2. Rate of Lung function change pre and post-nintedanib, with difference overall and by subgroup (N=123)

	n	Rate pre	95%CI	Rate post	95%CI	Difference	95%CI	p
FVC (ml)								
Overall	123	-239.86	-292.71 to -187.01	-88.79	-156.23 to -21.34	151.23	47.45; 255.01	0.004
Diagnosis								
fHP	42	-232.8	-313.8 to -151.8	-109.8	-219.6 to 0.05	125.4	-18.4 to 269.1	0.087
CTD-ILD	44	-190.8	-276.0 to -105.7	-66.3	-179.1 to 46.4	122.5	-47.7 to 292.7	0.158
Other	37	-281.1	-391.0 to -171.2	-113.1	-243.6 to 17.4	172.7	-25.8 to 371.2	0.088
CT pattern								
UIP	29	-246.3	-370.1 to -122.5	-120.6	-271.5 to 30.3	123.8	-94.3 to 342.0	0.266
Non-UIP	93	-225.5	-279.8 to -171.2	-87.1	-162.5 to -11.8	138.1	30.7 to 245.4	0.012
Sex								
Male	57	-295.9	-379.1 to -212.6	-100.7	-198.4 to -2.9	193.4	27.2 to 359.6	0.023
Female	66	-168.3	-215.3 to -121.4	-90.2	-180.7 to 0.3	79.9	-16.0 to 175.8	0.102
ppDLco (%)								
Overall	114	-6.06	-7.35 to -4.77	-2.13	-4.06 to -0.20	3.93	1.27 to 6.60	0.004
Diagnosis								
fHP	39	-7.5	-9.3 to -5.6	-2.5	-5.7 to 0.6	5	1.1 to 8.9	0.013
CTD-ILD	42	-3.9	-5.9 to -1.9	-3.3	-6.4 to -0.3	0.6	-3.9 to 5.1	0.803
Other	33	-6.7	-9.2 to -4.2	-0.1	-4.4 to 4.2	6.6	1.9 to 11.4	0.006
CT pattern								
UIP	27	-6.5	-8.8 to -4.2	-3.8	-7.7 to 0.2	2.6	-2.5 to 7.7	0.312
Non-UIP	86	-5.8	-7.2 to -4.3	-1.7	-3.9 to 0.5	4	1.0 to 7.1	0.009
Sex								
Male	53	-7.2	-8.9 to -5.4	-3.8	-6.4 to -1.1	3.4	-0.6 to 7.3	0.092
Female	61	-4.6	-6.3 to -3.0	-0.6	-3.2 to 2.0	4	0.8 to 7.2	0.014
Kco (%)								
Overall	108	-5.7	-8.36 to -3.04	-1.26	-5.18 to -2.65	4.43	-0.99 to 9.86	0.109
Diagnosis								
fHP	38	-8.6	-13.3 to -4.0	0.2	-6.4 to 6.7	9	-0.8 to 18.7	0.071
CTD-ILD	39	-4.4	-10.2 to 1.5	-2.1	-8.35 to 4.1	2.3	-8.2 to 12.8	0.666
Other	31	-4.2	-8.4 to 0.1	-2.9	-11.9 to 6.1	1.3	-6.3 to 8.9	0.732
CT pattern								
UIP	25	-6.5	-11.2 to -1.7	1.4	-6.7 to 9.4	8.1	-2.2 to 18.3	0.122
Non-UIP	82	-5.5	-8.7 to -2.3	-2.2	-6.8 to 2.3	3.3	-3.1 to 9.9	0.314
Sex								
Male	51	-7.3	-11.2 to -3.4	-5.4	-10.8 to 0.02	1.9	-6.1 to 9.9	0.647
Female	57	-4	-7.5 to -0.5	2.35	-2.9 to 7.6	6.2	-0.7 to 13.2	0.079

Rate of lung function change estimated from longitudinal multilevel models for repeat measures adjusted for age, sex, diagnostic group, radiologic pattern and early cessation of treatment (<12 months). Difference between groups estimated with restricted linear spline include knot at initiation.

Supplementary Table 3. Sensitivity analyses of rate of ppFVC change per year (N=122)

Sensitivity analysis	Rate pre %	95%CI	Rate post %	95%CI	Difference %	95%CI	p
ppFVC							
1. Overall	-6.91	-8.45 to -5.36	-2.57	-4.59 to -0.54	4.34	1.35 to 7.33	0.004
2. Time continuous/yr	-6.63	-8.47 to -4.79	-2.96	-5.18 to -0.74	3.67	0.32 to 7.02	0.032
3. Imputation I	-6.02	-8.27 to -3.77	-3.35	-5.68 to -1.03	2.67	-1.28 to 6.61	0.185
4. Imputation II	-5.25	-6.73 to -3.77	-2.75	-4.23 to 1.27	2.50	-0.07 to 5.06	0.057
5. Imputation III	-6.86	-8.29 to -5.42	-3.84	-5.27 to -2.40	3.02	0.72 to 5.32	0.010

1. Overall analysis: identical to primary analysis with use of percent predicted FVC as outcome.
2. Time continuous: timing of ppFVC record from nintedanib initiation modelled as continuous variable rather than discrete time point.
3. Imputation I: missing ppFVC imputed at cohort median per time point (pre, initiation, post).
4. Imputation II: missing ppFVC imputed as carried backward or forward from non-missing time point.
5. Imputation III: missing ppFVC imputed at 10% relative decline from pre-nintedanib to initiation and initiation to post-nintedanib.

Supplementary Table 4. Lung function according to changes in nintedanib dose

Nintedanib dose	**Change FVC (%) post-nintedanib**				**Difference in FVC change pre vs post nintedanib**			
	n	mean	SD	p	n	mean	SD	p
Maintained	51	-3.69	7.77		46	2.09	11.38	
Reduced	21	-0.80	7.60	0.154	17	4.91	8.51	0.357
	Change in DLco(%) post-nintedanib				**Difference in DLco change pre vs post-nintedanib**			
	n	mean	SD	p	n	mean	SD	p
Maintained	38	-2.89	6.49		33	3.53	8.07	
Reduced	16	-1.53	4.94	0.456	13	1.38	8.98	0.436
	Change in Kco(%) post-nintedanib				**Difference in Kco change pre vs post-nintedanib**			
	n	mean	SD	p	n	mean	SD	p
Maintained	36	-0.88	13.91		31	6.13	18.53	
Reduced	15	-4.16	7.66	0.395	10	-3.71	14.13	0.133

Supplementary Table 5. Lung function according to changes in concurrent immunosuppression

	Change FVC (%) post-nintedanib				**Difference in FVC change pre vs post nintedanib**			
	N	mean	SD	p	n	mean	SD	p
Immunosuppressant dose								
Increased	9	-4.19	9.93		9	-0.60	11.45	
Maintained	40	-3.55	7.57		32	1.89	11.05	
Reduced	23	-1.11	7.30	0.425	22	5.66	9.61	0.261
	Change in DLco(%) post-nintedanib				**Difference in DLco change pre vs post-nintedanib**			
	N	mean	SD	p	n	mean	SD	p
Immunosuppressant dose								
Increased	6	-1.45	7.29		6	4.70	11.25	
Maintained	31	-3.15	6.30		24	0.25	5.68	
Reduced	17	-1.63	5.35	0.652	16	6.27	9.49	0.065
	Change in Kco(%) post-nintedanib				**Difference in Kco change pre vs post-nintedanib**			
	N	mean	SD	p	n	mean	SD	p
Immunosuppressant dose								
Increased	6	5.08	16.06		6	10.53	26.43	
Maintained	28	-2.31	12.66		21	1.60	16.84	
Reduced	17	-3.52	10.46	0.337	14	4.02	15.91	0.570