Supplementary Material

GLPG1205 for idiopathic pulmonary fibrosis: a phase 2 randomised placebo-controlled trial

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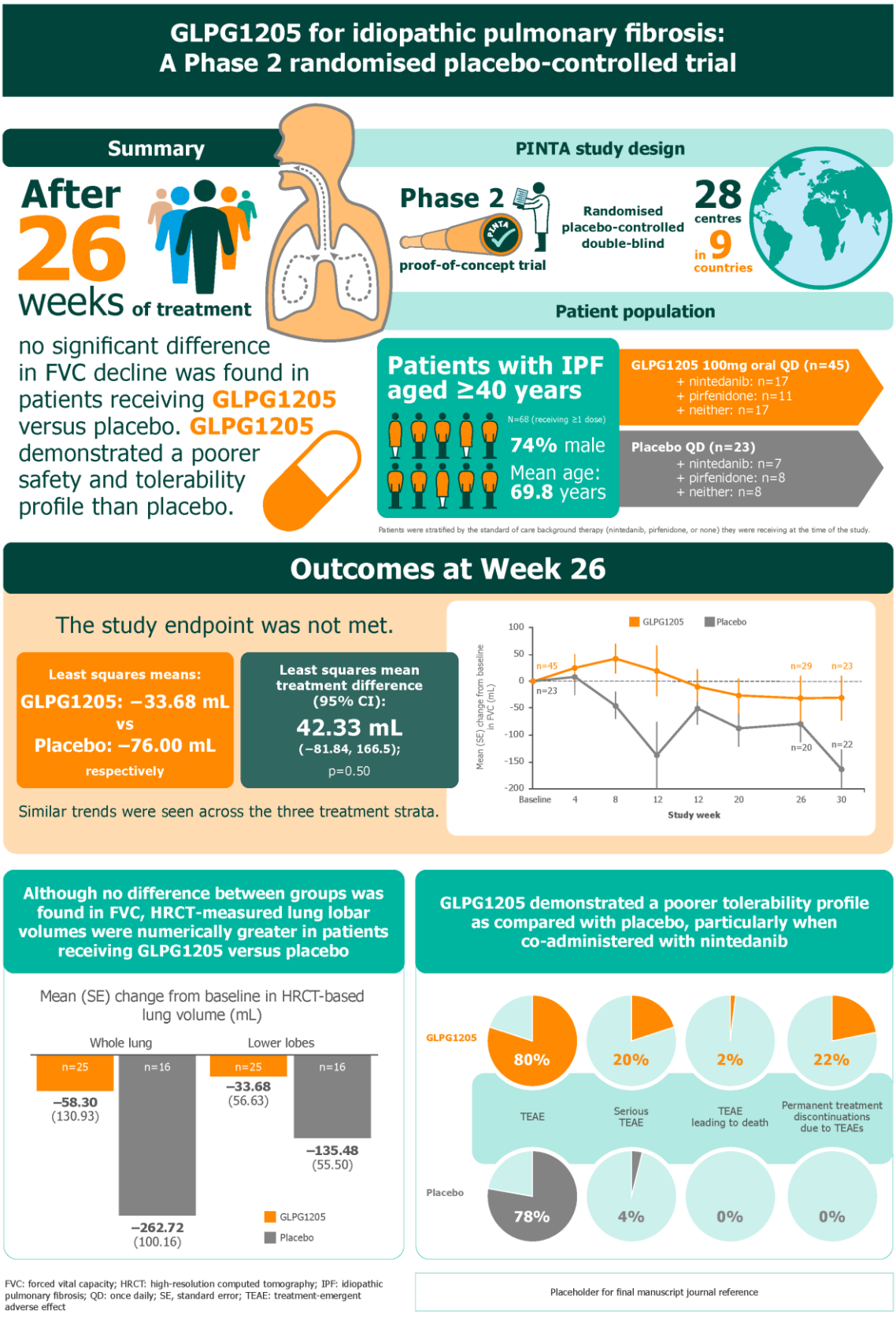
Table of Contents

Plain language summary

Idiopathic pulmonary fibrosis (IPF) is a long-term lung condition that worsens over time and is eventually fatal, with half of patients dying within 3–4 years of diagnosis. Only two drugs, pirfenidone and nintedanib, are currently approved as standard of care treatment for IPF. While both can slow down worsening of IPF, they do not entirely stop the disease and patients often experience side effects. GLPG1205 is a potential drug that functionally blocks a receptor known as G-protein-coupled receptor 84 (GPR84). GPR84 may be important in IPF.

A phase 2 clinical trial called PINTA (NCT03725852) investigated the efficacy and safety of GLPG1205 in 69 patients with IPF. Lung function was assessed by forced vital capacity (the maximum amount of air that can be forcibly exhaled from the lungs after fully inhaling) and lung volume imaging. On average, change in lung function did not differ in patients taking GLPG1205 compared with those taking placebo. A higher proportion of patients taking GLPG1205 versus those taking placebo experienced serious or severe side effects, particularly if they were also taking nintedanib. Additional studies are required to characterise the effect of targeting GPR84 in IPF.

Graphical abstract



FVC: forced vital capacity; HRCT: high-resolution computed tomography; IPF: idiopathic pulmonary fibrosis; QD: once daily; SE, standard error; TEAE: treatment-emergent adverse effect

Placeholder for final manuscript journal reference

Study protocol (NCT03725852)

The redacted study protocol is publicly available via ClinicalTrials.gov:

https://www.clinicaltrials.gov/ProvidedDocs/52/NCT03725852/Prot_000.pdf

Detailed eligibility criteria

To be included in the study, patients were required to have a diffusion capacity of lungs for carbon monoxide (D_{LCO}) ≥30% of predicted normal, corrected for haemoglobin; the ability to walk ≥150 meters during a 6-min walk test (6MWT); a stable condition and suitable for study participation based on medical history, physical examination, vital signs, 12-lead ECG, and laboratory evaluation; and an estimated minimum life expectancy ≥12 months for non-idiopathic pulmonary fibrosis (IPF)-related disease, based on the investigator's opinion. Patients receiving nintedanib or pirfenidone must have received a stable dose—defined as the highest tolerated dose—for ≥8 weeks prior to and during screening. Prednisone at a steady dose ≤10 mg/day, or equivalent glucocorticoid dose, was allowed (stabilised ≥4 weeks prior to screening and continued without variation of dose or regimen). Patients were excluded if they had any of the following: known hypersensitivity or history of allergic reaction to the investigational product; a current immunosuppressive condition (e.g. human immunodeficiency virus infection); blood test positive for hepatitis B surface antigen or hepatitis C virus antibody; history of malignancy within the past 5 years; clinically significant abnormalities detected on a 12-lead ECG of either rhythm or conduction; acute IPF exacerbation within 3 months of screening; lower respiratory tract infection requiring antibiotics within 4 weeks of screening; interstitial lung disease associated with known primary diseases and/or drugs; history of lung volume reduction surgery or lung transplant; unstable cardiovascular, pulmonary (other than IPF), or other disease within 6 months prior to or during screening; moderate-to-severe hepatic impairment; abnormal renal function, defined as estimated creatinine clearance <30 mL/min; major surgery within

3 months prior to screening or planned during the study period; and/or haemoglobin level <10 g/dL.

Patients were also excluded if they used any of the following non-evidence-based medications for IPF within 4 weeks before or during screening, or planned to use them during the study: warfarin, imatinib, endothelin receptor antagonists, azathioprine, cyclophosphamide, cyclosporine A, methotrexate, sildenafil, or prednisone at a steady dose >10 mg/day or equivalent glucocorticoid dose. Patients using known breast cancer resistance protein substrates, dual cytochrome P450 (CYP)3A4 and CYP2C19 inhibitors, or CYP3A4 or CYP2C19 strong inducers were excluded if screening or the study fell within five half-lives of the treatment, or their use was planned during the study.

COVID-19 pandemic: Study accommodations, impact and sensitivity analysis

Reasonable modifications to assessment timings were made to account for the impact of the coronavirus disease 2019 (COVID-19) pandemic. Where in-person visits to the study centre could not be made for safety reasons, remote visits (e.g. phone calls, virtual visits) were conducted. Treatments were provided to patients via direct-to-patient shipping and treatment schedules were unaffected, as were laboratory data analyses and data cleaning activities.

Overall, 23 visits for 18 patients were conducted remotely/via phone; during these visits, patients' safety was evaluated but assessments, including blood sampling, spirometry, 6MWT, SGRQ, lung volumes by high-resolution computed tomography (HRCT), and D_{LCO}, were not possible. Assessments planned as part of the week 26 visit (including the primary endpoint) that could not be conducted remotely were delayed for three patients (one in the GLPG1205 group and two in the placebo group) and assigned to the week 30 analysis window. Across the whole study, 14 visits (week 12 for one patient, week 20 for one patient, week 26 for three patients and week 30 for nine patients) were performed outside of the prespecified window as per the original study protocol.

Results of the sensitivity analysis conducted to evaluate the impact of delayed week 26 primary end-point assessments due to the COVID-19 pandemic did not differ substantially from those of the primary analysis. Week 26 least squares mean change in FVC from baseline was –16.70 (95% CI –94.80–61.41) mL for GLPG1205 and –86.02 (95% CI –177.31–5.28) mL for placebo (least squares mean treatment difference 69.32 [95% CI –51.22–189.85] mL; p=0.25).

Measurement of lung lobar volumes by HRCT

Lobar volume was obtained by identifying and grouping voxels that represent air in the lungs. Lung volume in litres was determined from HRCT scans at full inspiration. Additionally, individual lobar volumes were determined by identifying the fissure planes on the HRCT images.

Determination of study population size and secondary efficacy analyses

A study population size of approximately 60 patients (GLPG1205, n=40; placebo, n=20) was considered appropriate, based on the following assumptions: a 50:50 balance of patients on nintedanib/pirfenidone or neither standard of care (SoC) treatment; dropout rate of 10%; and a common standard deviation (SD) of 200 mL for FVC change from baseline to week 26. With true treatment differences for FVC change from baseline to week 26 of 50 mL with nintedanib/pirfenidone and 80 mL with neither SoC, the probability of observing a treatment effect >40 mL in the total study population, using a two-sided 5% significance level, was 67%, and the probability of observing a treatment effect >20 mL was 78%.

Secondary efficacy analyses were performed using ANCOVA (change from baseline in: FVC % pred, 6MWT results and SGRQ total score), a log-rank test (treatment effects on time to death and/or hospitalisation), a Fisher exact test (proportion of SGRQ responders), or were reported descriptively. Continuous variables were reported using descriptive statistics (n, mean [SD], median [interquartile range; IQR]). Categorical variables were reported as frequencies and percentages. Treatment compliance was calculated based on the total number of doses planned and the total number taken, according to patient diary cards.

Table S1 Summary of study assessments

Study time-point	Screening (day −28 to day −1)	Baseline (day 1)	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 26[#]	Early end of treatment	Week 30 follow-up or early end of study
Spirometry[¶]	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓
SGRQ[+]		✓				✓			✓	✓	
D_{LCO}[†]	✓								✓		
6MWT[‡]	✓	✓							✓	✓	
HRCT[§]		✓							✓	✓	

6MWT: 6-minute walk test; D_{LCO}: diffusing capacity for the lungs for carbon monoxide; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; HRCT: high-resolution computed tomography; IPF: idiopathic pulmonary fibrosis; SGRQ: St. George's Respiratory Questionnaire. [#]: week 26 represents the regular end of treatment; [¶]: pulmonary function was measured using standardised equipment and was evaluated by a central reader. Measured parameters were FVC, FVC % pred, FEV_1, FEV_1 % pred, FEV_1/FVC ratio and forced expiratory flow between 25% and 75% of exhaled volume ($FEF_{25–75}$). Spirometry assessments were performed at the study centre to assess pulmonary function, which was measured in a standardised manner using standardised equipment, before bronchodilation and blood/urine sampling. Results were transmitted electronically and evaluated by a central reader; [+]: the total SGRQ score ranges from 0 to 100, with higher scores indicating poorer quality of life. A reduction of 4 units in SGRQ total score was used to define a minimal clinically important difference (Ref 1); [†]: D_{LCO} measurement was mandatory at screening; it was conducted again at week 26, but only requested by protocol if a D_{LCO} machine was available on site; [‡]: functional exercise capacity was assessed according to American Thoracic Society recommendations (Ref 2); [§]: measurements of lung lobar volumes at full inspiration were evaluated by a central reader using established methods to characterise IPF disease progression (Ref 3). HRCT was performed at week 26 or (early) end of treatment.

Ref 1. Jones PW. St. George's Respiratory Questionnaire: MCID. *COPD* 2005; 2: 75–79.

Ref 2. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166: 111–117.

Ref 3. Clukers J, Lanclus M, Mignot B, et al. Quantitative CT analysis using functional imaging is superior in describing disease progression in idiopathic pulmonary fibrosis compared to forced vital capacity. *Respir Res* 2018; 19: 213.

Table S2 Summary of TEAEs by SoC stratification (full analysis set)

	SoC stratification					
	GLPG1205 100 mg + pirfenidone (n=11)	**Placebo + pirfenidone (n=8)**	**GLPG1205 100 mg + nintedanib (n=17)**	**Placebo + nintedanib (n=7)**	**GLPG1205 100 mg + neither (n=17)**	**Placebo + neither (n=8)**
TEAEs	7 (63.6)	7 (87.5)	16 (94.1)	6 (85.7)	13 (76.5)	5 (62.5)
Serious TEAEs	0	0	7 (41.2)	1 (14.3)	2 (11.8)	0
TEAEs leading to death	0	0	1 (5.9)	0	0	0
TEAEs with worst severity						
Mild	1 (9.1)	3 (37.5)	3 (17.6)	2 (28.6)	6 (35.3)	2 (25.0)
Moderate	4 (36.4)	4 (50.0)	4 (23.5)	3 (42.9)	6 (35.3)	3 (37.5)
Severe	2 (18.2)	0	5 (29.4)	1 (14.3)	1 (5.9)	0
Life-threatening	0	0	3 (17.6)	0	0	0
Death	0	0	1 (5.9)	0	0	0
TEAEs related to GLPG1205/placebo	5 (45.5)	2 (25.0)	12 (70.6)	1 (14.3)	3 (17.6)	0
TEAEs related to SoC	4 (36.4)	3 (37.5)	8 (47.1)	1 (14.3)		
Study treatment GLPG1205/placebo						
Reduced[#]	0	0	2 (11.8)	1 (14.3)	0	0
Temporarily stopped	1 (9.1)	2 (25.0)	2 (11.8)	0	1 (5.9)	0
Permanently stopped	2 (18.2)	0	6 (35.3)	0	2 (11.8)	0
SoC treatment						
Reduced[#]	0	0	1 (5.9)	0		
Temporarily stopped	0	1 (12.5)	3 (17.6)	0		
Permanently stopped	2 (18.2)	1 (12.5)	2 (11.8)	0		

Data are presented as n (%). SoC: standard of care; TEAE, treatment-emergent adverse event. [#]: dose reduction was not preceded by treatment interruption for the same reported event. In addition, three patients receiving GLPG1205 100 mg (two on a background of nintedanib and one on a background of pirfenidone) and none on placebo interrupted treatment because of TEAEs and restarted on a reduced dose. Regarding SoC treatment interruptions due to a TEAEs, no subject had a consecutively reduced dose due to the same event.

Table S3 Serious TEAEs and TEAEs leading to treatment discontinuation

Case	Event	Intensity	SAE	Led to IP discontinuation	Outcome[#]
GLPG1205 100 mg + nintedanib SoC					
1	Interstitial lung disease	Death	Yes	No	Fatal
2	Myocardial ischemia	Severe	Yes	No	Resolved
	Angina pectoris	Severe	Yes	No	Resolved
3	Headache	Severe	Yes	No	Resolved
	Neck pain	Moderate	Yes	No	Resolved
4	Intervertebral disc protrusion	Severe	Yes	No	Resolved
	Post-procedural infection	Severe	Yes	No	Resolved
5	Normocytic anaemia	Severe	Yes	No	Resolving
6	Neutropenia[¶]	Life-threatening	Yes	Yes	Resolved
	Headache	Moderate	No	Yes	Resolved
	Nausea	Moderate	No	Yes	Resolved
	Vomiting	Moderate	No	Yes	Resolved
7	General physical health deterioration	Severe	Yes	Yes	Resolved
8	ALT increased	Life-threatening	No	Yes	Resolved
	AST increased	Severe	No	Yes	Resolved
9	ALT increased	Life-threatening	No	Yes	Resolved
	AST increased	Life-threatening	No	Yes	Resolved
	GGT increased	Severe	No	Yes	Resolved
10	Diarrhoea infectious	Moderate	No	Yes	Resolving
11	Diarrhoea	Mild	No	Yes	Resolved
	Nausea	Mild	No	Yes	Resolved
	Asthenia	Mild	No	Yes	Resolved
GLPG1205 100 mg + pirfenidone SoC					
12	Dyspnoea	Severe	No	Yes	Resolved
	Fatigue	Severe	No	Yes	Resolved
	Decreased appetite	Mild	No	Yes	Resolved
	Nausea	Mild	No	Yes	Resolved
13	Nausea	Moderate	No	Yes	Resolved
	Asthenia	Mild	No	Yes	Resolved
	Decreased appetite	Mild	No	Yes	Resolved
	Dizziness	Mild	No	Yes	Resolved
	Abdominal pain (upper)	Mild	No	Yes	Resolved
	Headache	Mild	No	Yes	Resolved
	Diarrhoea	Mild	No	Yes	Resolved

GLPG1205 100 mg + neither SoC					
14	Gastrointestinal viral infection	Moderate	Yes	Yes	Resolved
15	Breast cancer	Severe	Yes	No	Resolving
	Nausea	Moderate	No	Yes	Resolved
Placebo + nintedanib SoC					
16	Bronchitis	Severe	Yes	No	Resolved
	Bronchitis	Mild	Yes	No	Resolved

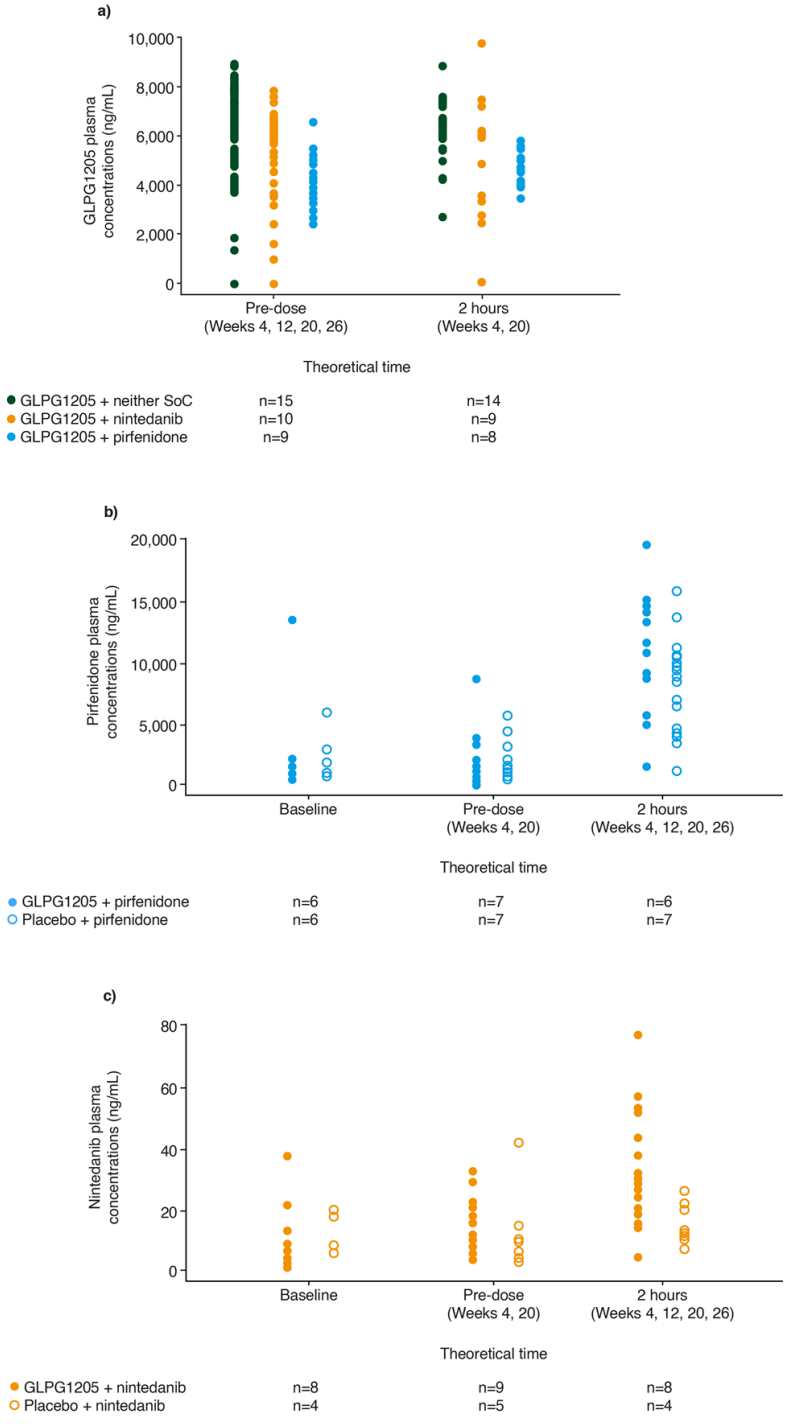
ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: γ-glutamyltransferase; IP: investigational product; SAE: serious adverse event; SoC: standard of care; TEAE: treatment-emergent adverse event. [#]: outcome of the last event; [¶]: medical history relevant to the SAE included hairy cell leukaemia. This patient was diagnosed with hairy cell leukaemia 25 years prior to the start of the study. The patient had been treated with interferon and 2-CdA for 7 years; the hairy cell leukaemia was considered inactive by the investigator at start of the study.

Table S4 Change from baseline over 26 weeks in image-based lung lobar volume (L) measured by HRCT at full inspiration (LMM; full analysis set)

	GLPG1205 100 mg (n=45)	Placebo (n=23)	Treatment difference
Average: All zones			
LS mean±SE	–0.011±0.0112	–0.050±0.0141	0.039±0.0180
95% CI	–0.033–0.011	–0.078, –0.023	0.004–0.075
p-value			0.031
Average: RUL, RML, LUL			
LS mean±SE	–0.009±0.0144	–0.040±0.0181	0.031±0.0231
95% CI	–0.037, 0.019	–0.076, –0.005	–0.014–0.077
p-value			0.18
Average: RLL, LLL			
LS mean±SE	–0.015±0.0177	–0.065±0.0222	0.051±0.0284
95% CI	–0.049–0.020	–0.109, –0.021	–0.005–0.107
p-value			0.077

Data are averaged over lung regions (e.g. average RLL and LLL values are calculated as [LS mean RLL + LS mean LLL]/2). Results are based on an LMM including the three-way interaction treatment-by-time-by-zone as fixed effects and a random slope for zone by subject. The treatment effect is determined by using LS mean contrasts comparing the change from baseline between treatment groups by predefined locations. CI: confidence interval; HRCT: high-resolution computed tomography; LLL: left lower lobe; LMM: linear mixed model; LS: least squares; LUL: left upper lobe; RLL: right lower lobe; RML: right middle lobe; RUL: right upper lobe; SE: standard error.

Figure S1 Plasma concentrations of (**a**) GLPG1205 alone or on top of local SoC background therapy (nintedanib or pirfenidone), pre- and 2 h post-dose of study treatment; (**b**) pirfenidone when administered with GLPG1205 or placebo at baseline (before first dose of study treatment), pre- and 2 h post-dose of SoC; and (**c**) nintedanib when administered with GLPG1205 or placebo at baseline (before first dose of study treatment), pre- and 2 h post-dose of SoC



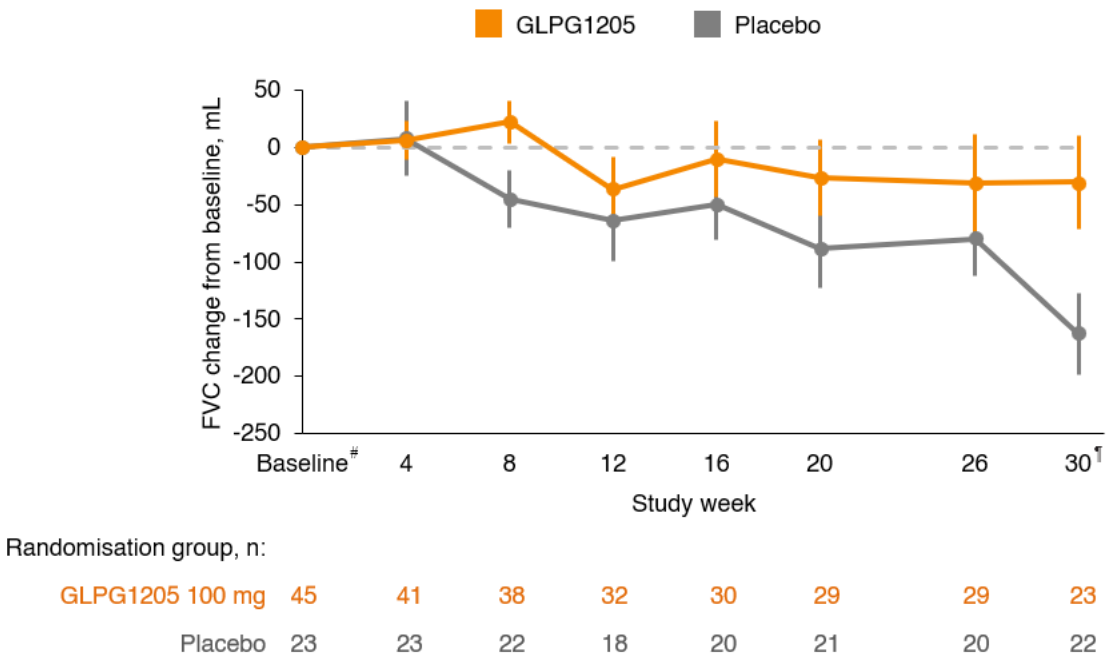
Samples at baseline and weeks 4, 12, 20 and 26 were collected prior to dosing with study treatment and, if applicable, either prior to SoC intake (baseline and weeks 4 and 20) or after SoC intake (weeks 12 and 26). Additionally, at weeks 4 and 20, samples were collected approximately 2 h after dosing with study treatment and/or SoC, if applicable. Plasma concentrations were also evaluated at week 30 (no study treatment given). Plasma concentrations were determined using a validated liquid chromatography–tandem mass spectrometry analytical method (Timmis H, Van Kaem T, Desrivot J, et al. GLPG1205, a GPR84 modulator: Safety, pharmacokinetics, and pharmacodynamics in healthy subjects. *Clin Pharmacol Drug Dev* 2021;10(9):994–1006).

Pre-dose samples for GLPG1205 were included if the sample date/time was >20 h after the preceding GLPG1205 intake (and prior to the next GLPG1205 intake) and 2-h post-dose samples were included if they were taken 1–3 h after the preceding GLPG1205 intake. Samples taken after a relevant GLPG1205 dose interruption or reduction were excluded. Pre-dose samples for nintedanib/pirfenidone were included if the sample date/time was before intake on the same day, and 2-h post-dose samples were included if they were taken 1–3 h after the preceding nintedanib/pirfenidone intake. Samples were only included if the patients were on nintedanib/pirfenidone background therapy at baseline and if the patient was on a stable nintedanib/pirfenidone target dose for at least 4 days. The number of circles represent the number of samples provided by n patients at a given time-point (therefore, in some instances, more than one sample was taken from a single patient).

The pharmacokinetic analysis did not consider the timing of GLPG1205 dosing versus SoC dosing. To overcome this, an additional population pharmacokinetic covariate analysis confirmed that plasma concentrations of GLPG1205 were not affected by coadministration of nintedanib or pirfenidone (data on file). Regarding the effect of GLPG1205 on SoC drug concentrations, potential variability of the dosing interval was limited by analysing GLPG1205 at steady state and by its long half-life (~90 h for once daily oral GLPG1205 100 mg after multiple doses), showing small fluctuations between the minimum and maximum plasma drug concentrations.

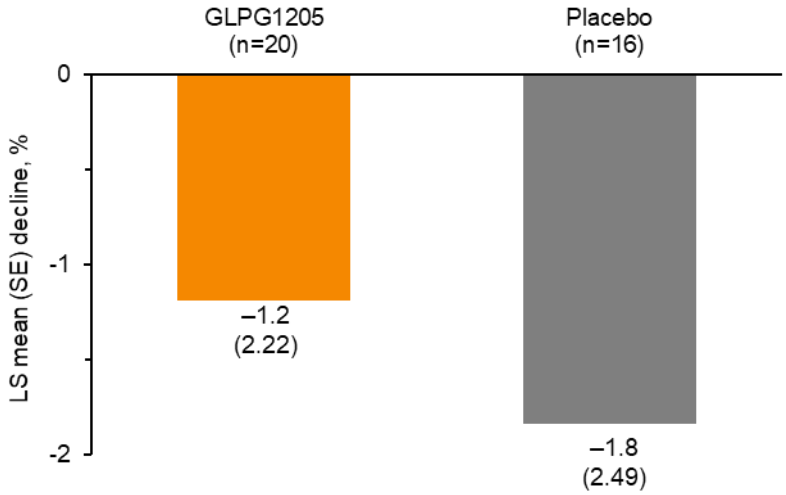
Plasma concentrations of GLPG1205 were not affected by coadministration of nintedanib or pirfenidone, as confirmed by population pharmacokinetic covariate analysis (supplementary figure S1). Pirfenidone plasma concentrations did not appear to be affected by coadministration with GLPG1205 at 2 h post-dose of SoC (median [IQR]: 11,200 [8,025–14,225] ng/mL with GLPG1205 and 9,005 [4,708–10,625] ng/mL with placebo). Coadministration of GLPG1205 with nintedanib resulted in numerically higher median (IQR) plasma concentrations of nintedanib at 2 h post-dose of SoC (28.4 [18.4–43.3] ng/mL) than did administration of nintedanib alone (12.2 [10.6–18.5] ng/mL), although substantial between-patient variability was observed and the investigated pharmacokinetic sample set was limited. Plasma levels of GLPG1205 were unaffected by coadministration with nintedanib or pirfenidone, and there was no evidence of GLPG1205 coadministration resulting in a drug–drug interaction affecting pirfenidone. SoC: standard of care.

Figure S2 Mean forced vital capacity by time in overall population and excluding outliers



The post hoc analysis excluding outliers found one outlier in the GLPG1205 group at weeks 4 and 8 and two outliers in each treatment group at week 12, resulting in a numerically less pronounced difference between groups. There were no outliers at week 26; thus, the primary endpoint results were unaffected by outliers. Error bars represent standard error; outliers were defined as measurements with an absolute change from baseline in forced vital capacity >600 mL. #: baseline values were defined as the mean of the analysis values before first treatment dose; ¶: safety follow-up visits were conducted at week 30.

Figure S3 Change from baseline in D_{LCO} % pred corrected



Baseline was defined as the last non-missing value before first dose of GLPG1205 or placebo.

D_{LCO}: diffusion capacity of lungs for carbon monoxide; LS: least squares; SE: standard error.