Supplementary Online Content

Raghu G, van den Blink B, Hamblin MF, et al. Effect of recombinant human pentraxin-2 vs placebo on change in forced vital capacity in patients with idiopathic pulmonary fibrosis: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2018.6129

eAppendix. Methods

Results

This supplementary material has been provided by the authors to give readers additional information about their work.

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Formatted for: Journal of the American Medical Association

Type: Clinical Trial

Tables and Figures: Maximum of 5 (combined, including CONSORT flow diagram); Currently 5 in the main body with 6 Supplementary tables and figures

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METHODS

Complete Patient Inclusion Criteria

Eligible patients were required to meet the following criteria to be enrolled in the study:

1. Age 40 to 80 years at the time of signing consent
2. The diagnosis of idiopathic pulmonary fibrosis (IPF) was in accordance with the criteria used in the INPULSIS clinical trials.[1] This included the 2011 ATS/ERS/JRS/ALAT criteria.[2] In the absence of a surgical lung biopsy, HRCT images were considered consistent with usual interstitial pneumonia if either criteria A, B, and C, or criteria A and C, or criteria B and C below were met:
    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, is less extensive than reticular opacity pattern
3. If receiving pirfenidone or nintedanib, not both, the patient must have been on a stable dose for at least 3 months prior to screening without increase in the percentage of predicted forced vital capacity (FVC) value on two consecutive pulmonary function tests, including screening tests
4. If not currently receiving pirfenidone or nintedanib, patient must have stopped pirfenidone or nintedanib for at least 4 weeks prior to baseline
5. FVC ≥50% and ≤90% of predicted
6. Hemoglobin-corrected diffusion capacity of carbon monoxide (Hb-corrected D_{LCO}) ≥25% and ≤90% of predicted

7. Minimum distance covered on the 6-minute walk test of 150 meters with or without supplemental oxygen supplementation
8. Forced expiratory volume in 1 second (FEV_1)/FVC ratio >0.70
9. Women of child bearing potential, defined as a sexually mature woman not surgically sterilized or not post-menopausal for at least 24 consecutive months if ≤55 years or 12 months if >55 years, must have a negative serum pregnancy test within four weeks prior to the first dose of study drug and must agree to use highly effective methods of birth control throughout the study and up to 30 days after the study and up to 90 days for partners of child bearing potential of male participants. Highly effective methods of contraception include combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation by oral, intravaginal, or transdermal administration; progestogen-only hormonal contraception associated with inhibition of ovulation by oral, injectable, or implantable administration; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; partner vasectomy, and total abstinence (only if total abstinence is the preferred method and usual lifestyle of the subject). Adequate contraceptive use should be continued until 28 days after the final dose of the study drug.
10. Patient has a life expectancy of at least 9 months
11. Patient, according to the investigator's best judgment, can comply with the requirements of the protocol
12. Patient and the treating physician considered all medicinal treatment options and/or possibly a lung transplantation prior to considering participation in the study

13. If the patient is listed for lung transplantation, the anticipated wait time at the site is beyond the need to complete the study protocol visits
14. Written informed consent to participate in the study

Complete Patient Exclusion Criteria

Patients were ineligible to participate if they met any of the following criteria:

1. Has emphysema ≥50% on high-resolution computed tomography (HRCT) or the extent of emphysema is greater than the extent of fibrosis according to the reported results of the most recent HRCT
2. A history of cigarette smoking within the 3 months prior to enrollment
3. Received investigational therapy for IPF within 4 weeks before baseline
4. Received systemic corticosteroids equivalent to prednisone >10 mg/day or equivalent within 2 weeks of baseline
5. Received immuno-suppressants (eg, azathioprine, cyclophosphamide, or cyclosporine or other immunosuppressants including those used after organ transplant) within 4 weeks of baseline
6. A history of malignancy within the previous 5 years, with the exception of basal cell skin neoplasms. In addition, a malignant diagnosis or condition first occurring prior to 5 years must be considered cured, inactive, and not under current treatment.
7. Any concurrent condition other than IPF that, in the Investigator's opinion, is unstable and/or would impact the likelihood of survival for the study duration or the patient's ability to complete the study as designed, or may influence any of the safety or efficacy assessments included in the study

8. A baseline resting oxygen saturation of <89% by finger pulse oximetry on room air or with supplemental oxygen
9. Unable to refrain from use of the following:
    a. Short acting bronchodilators on the day of and within 12 hours of pulmonary function, D_{LCO}, and 6-minute walk assessments
    b. Long acting bronchodilators on the day of and within 24 hours of these assessments
10. Known post-bronchodilator (short-acting beta agonist–albuterol or salbutamol) increase in FEV_1 of >10% and in FVC of >7.5%
11. Pregnant and/or lactating

Randomization

The unblinded pharmacist registered patients using an interactive voice-response system (IVRS) system. The IVRS assigned each patient a sequential and unique number. Once assigned, a patient number could not be reused. Prior to randomization, the investigator ensured that the patient continued to meet the inclusion criteria and was eligible for study participation, after which the unblinded pharmacist accessed IVRS for randomization and study drug assignment.

High-Resolution Computed Tomography

High-resolution Computed Tomography (HRCT) was performed at the baseline and Weeks 28, and weeks 76 and 128 visits for patients continuing treatment in the extension. Spirometry will be performed at selected sites to ensure that full inspiration HRCT is at Total Lung Capacity (TLC). HRCT was performed with the patient in the supine position and at full inspiration.

Contiguous CT volumetric acquisition will be obtained according to a specified protocol. HRCT scans will be compared using a standardized reading protocol and software to assess treatment-related changes in lung fibrosis.

Respiratory Decline Events

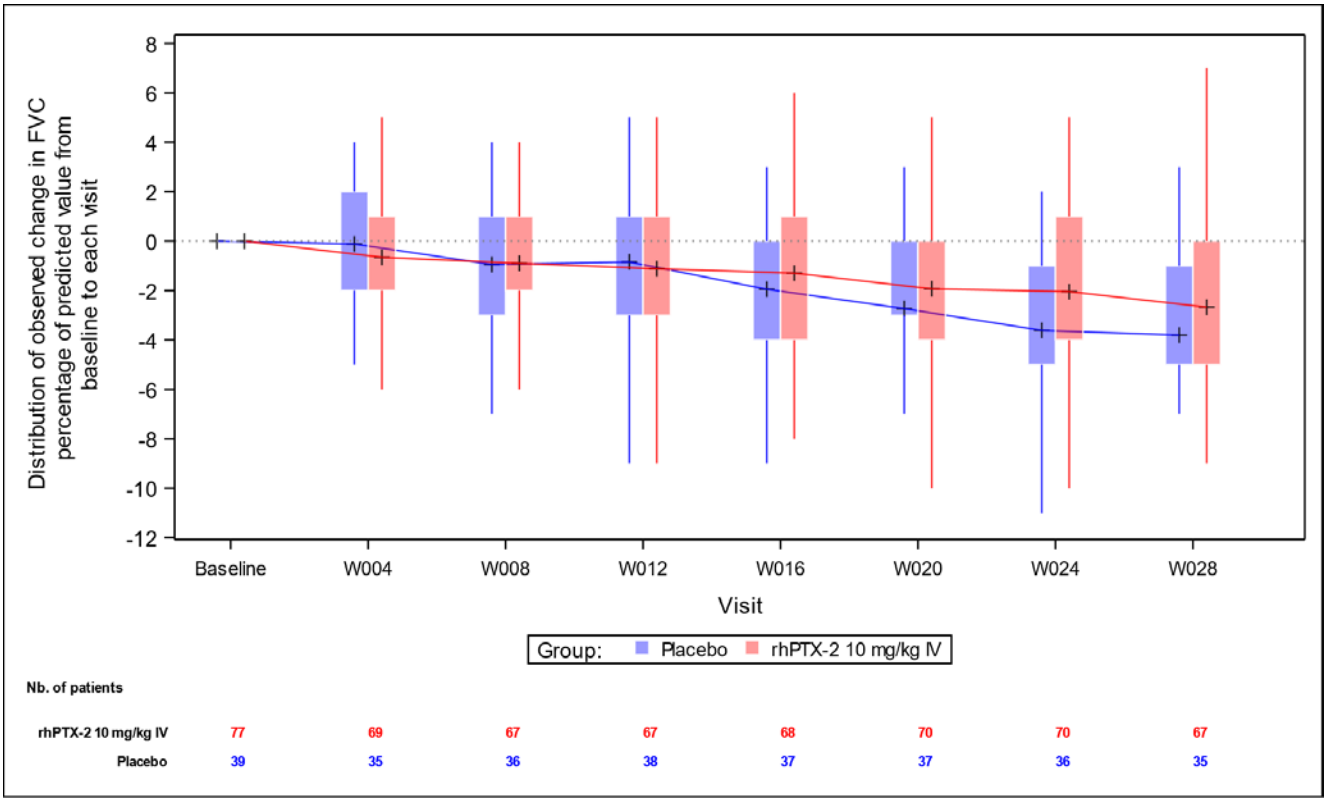
In this study, respiratory decline events were defined as any unscheduled visits to a healthcare professional or urgent care for a deterioration in respiratory status, or hospitalization due to a worsening or exacerbation of respiratory symptoms. All respiratory decline events were further characterized according to the definitions of IPF-related acute exacerbation by Collard et al.,[3,4] which included the following:

- Acute onset of symptoms (<30 days in duration)
- New radiographic abnormalities (bilateral ground glass or consolidation on HRCT with no pneumothorax or pleural effusion)
- The absence of an identified infectious etiology by routine clinical practice
- Exclusion of alternative causes by routine clinical practice, including left heart failure, pulmonary embolism, or identifiable cause of acute lung injury

RESULTS

eFigure 1. Box Plots of Observed Change in Forced Vital Capacity Percentage of Predicted Value from Baseline to Week 28. Distribution of observed change in FVC percentage of predicted value from baseline to week 28 (Panel A) and distribution of observed change in FVC percentage of predicted value at week 28 with individual observed data (Panel B).

A



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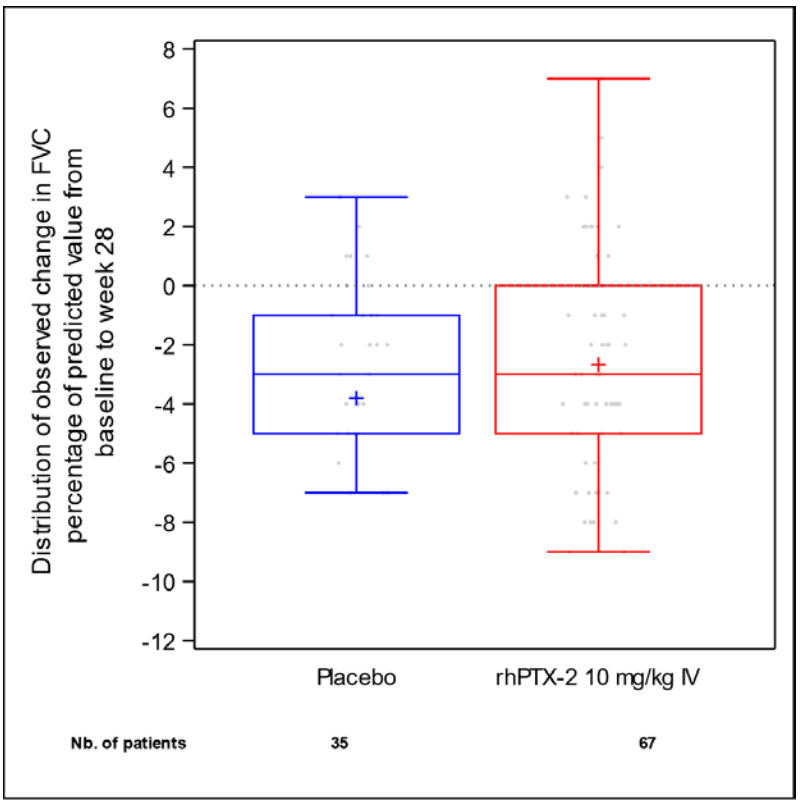
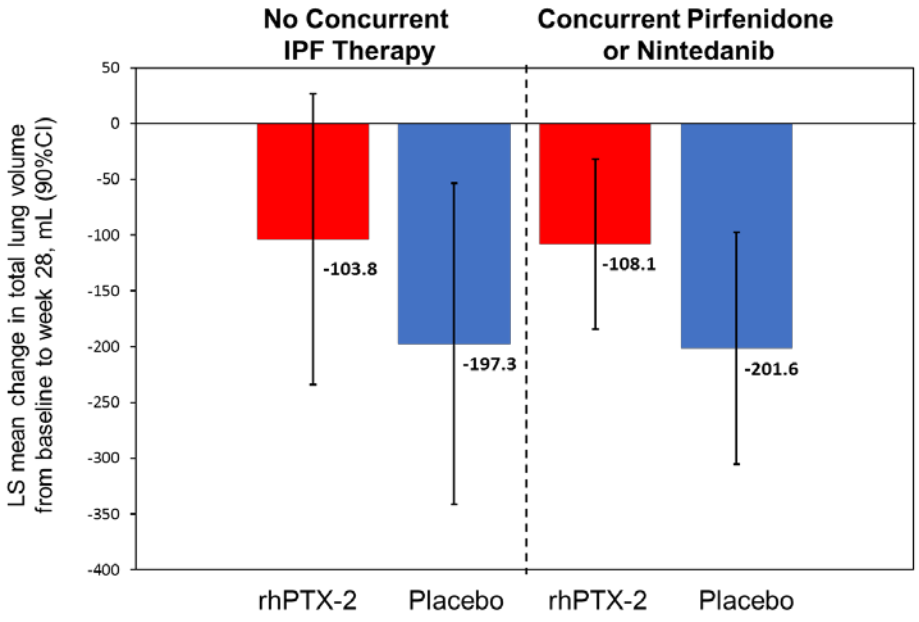


FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; rhPTX-2, recombinant human pentraxin-2.

eFigure 2. Least-Squares Mean (Secondary End Point) and Box Plot of Observed Change from Baseline to Week 28 in Total Lung Volume, Percentage of Normal Lung Volume, and Percentage of Interstitial Lung Abnormalities by Background Therapy Status. Least-squares mean change in total lung volume (Panel A), percentage of normal lung volume (Panel B), and percentage of interstitial lung abnormalities (Panel C). Distribution of observed change in total lung volume (Panel D), percentage of normal lung volume (Panel E), and percentage of interstitial lung abnormalities (Panel F).

A



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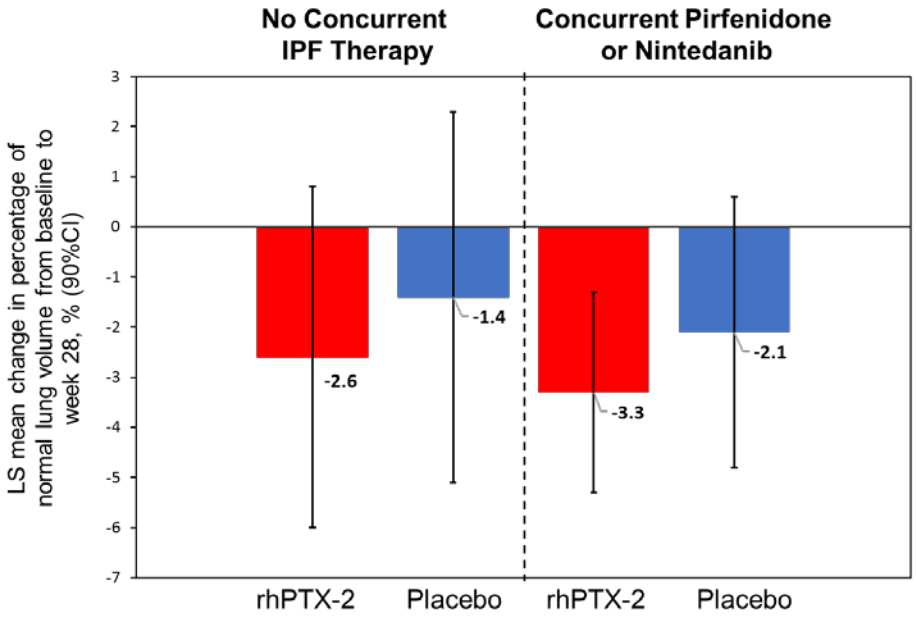

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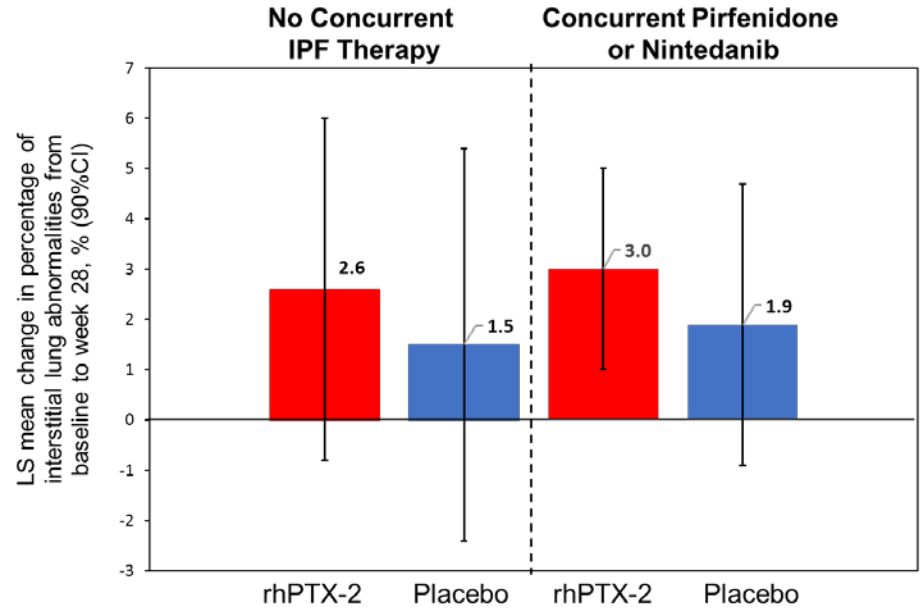

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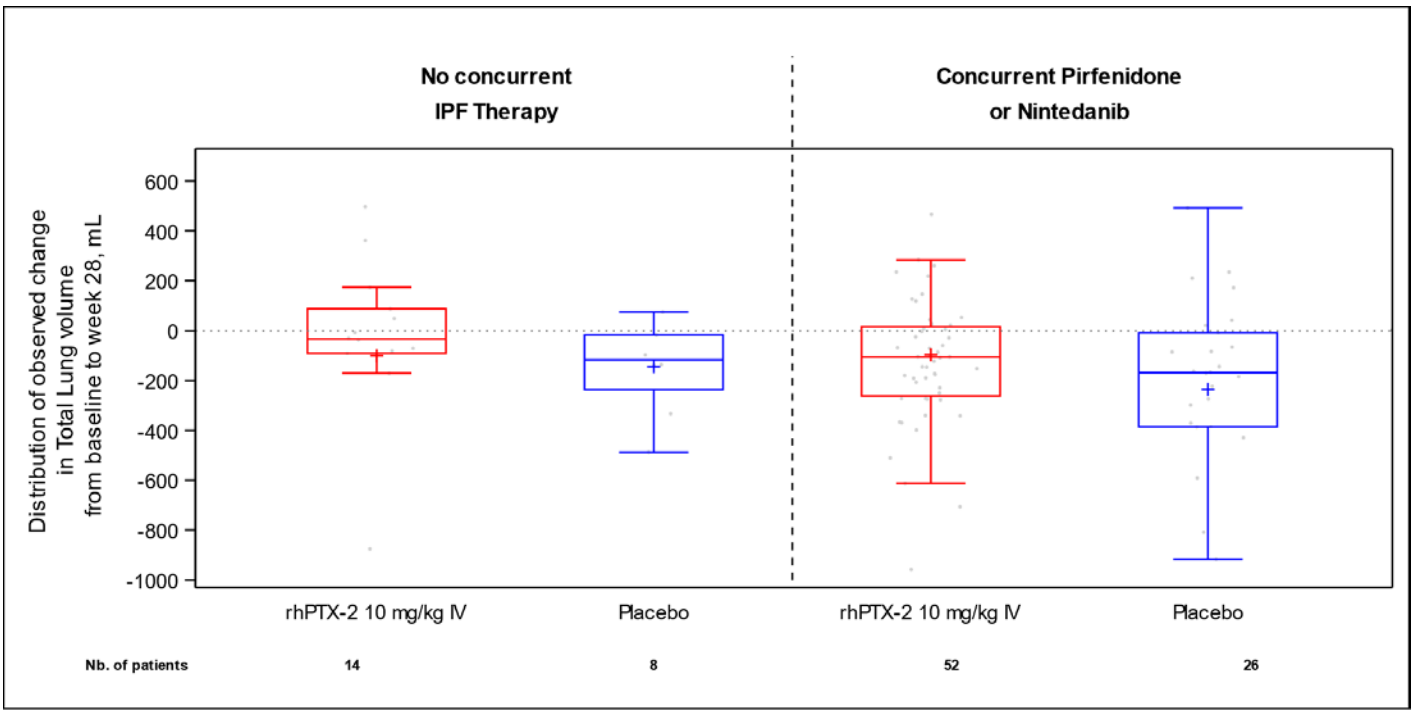

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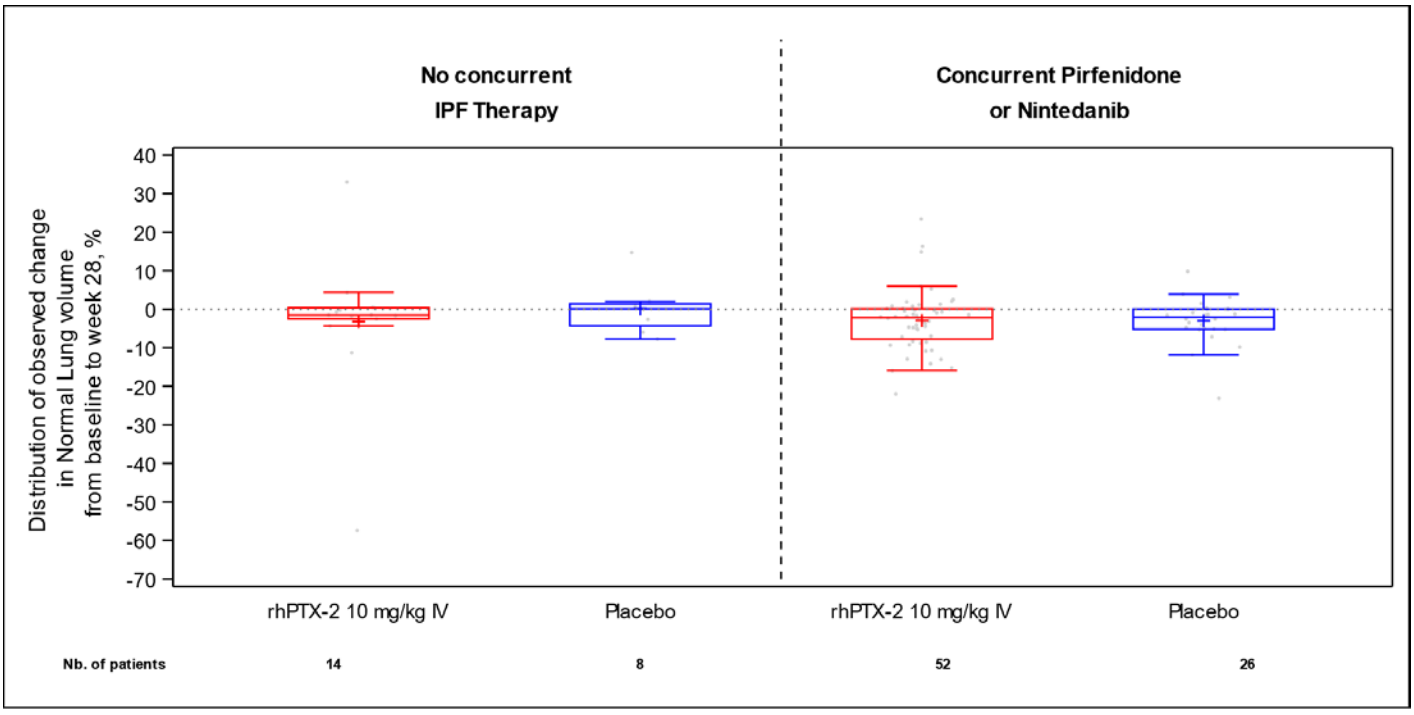

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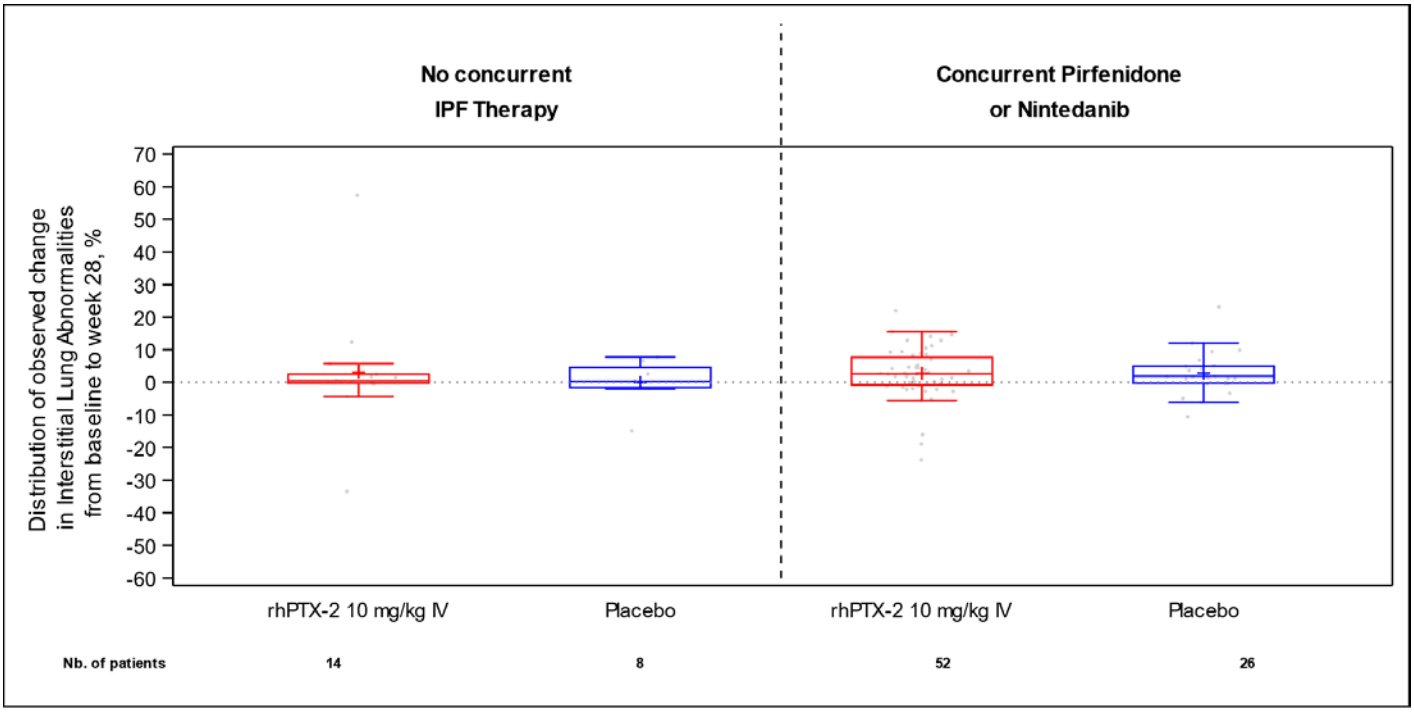
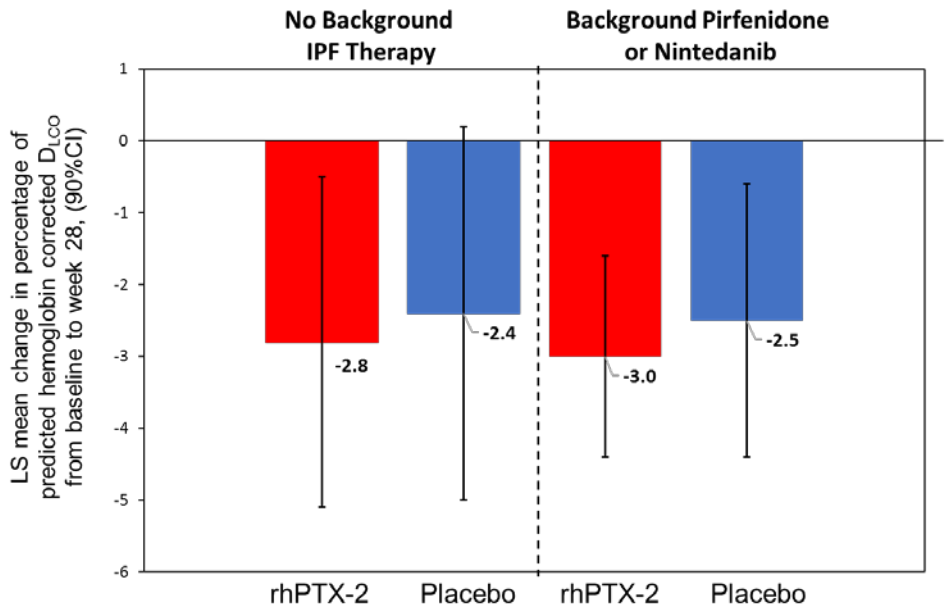


CI, confidence interval; IPF, idiopathic pulmonary fibrosis; LS, least squares; rhPTX-2, recombinant human pentraxin-2.

eFigure 3. Least-Squares Mean (Secondary End point) and Observed Mean Change from Baseline to Week 28 in D_{LCO} by Background Therapy Status. Least-squares mean change in D_{LCO} (Panel A) and distribution of observed change in D_{LCO} (Panel B).

A



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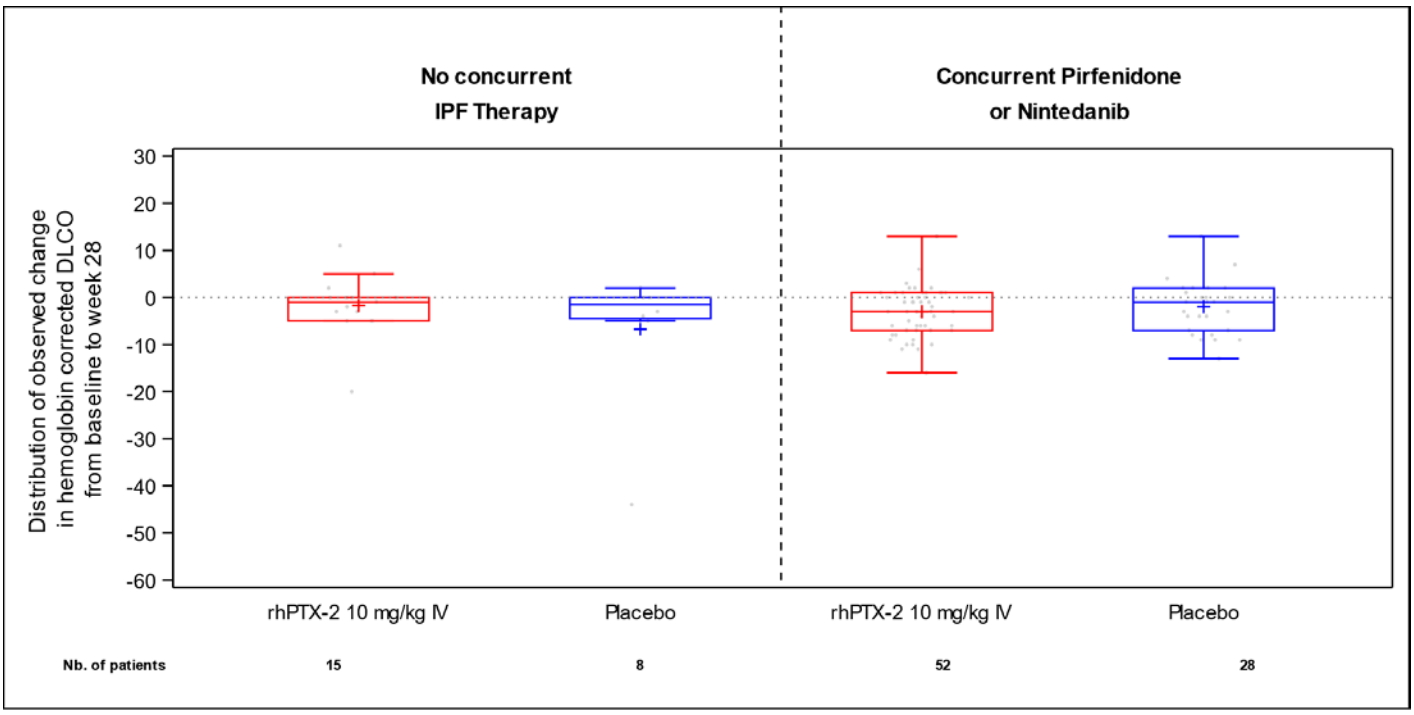
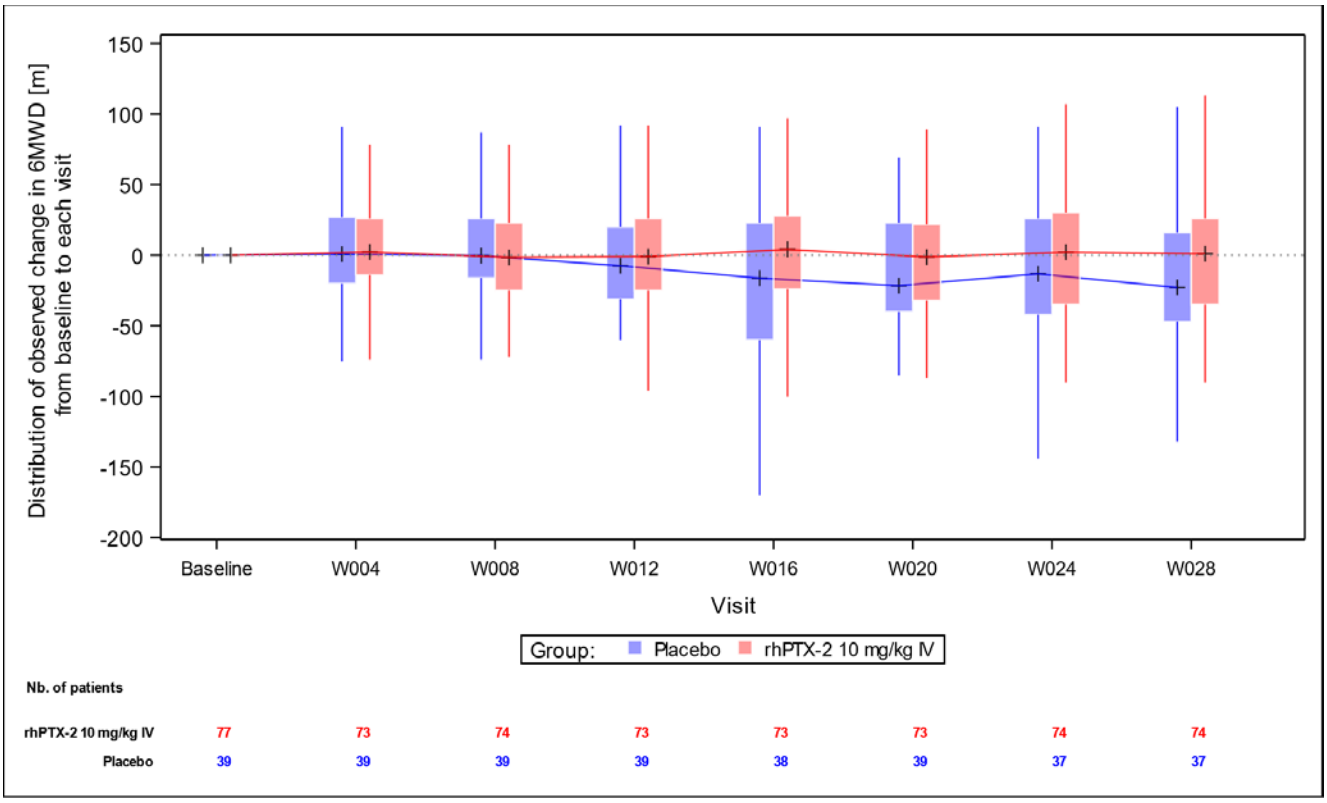


CI, confidence interval; D_{LCO}, diffusing capacity of the lungs for carbon monoxide; IPF, idiopathic pulmonary fibrosis; LS, least squares; rhPTX-2, recombinant human pentraxin-2.

eFigure 4. Box Plots of Observed Change in the 6-minute Walk Test from Baseline to Week 28. Distribution of observed change in 6-minute walk distance from baseline to week 28 (Panel A) and distribution of observed change in 6-minute walk distance at week 28 with individual observed data (Panel B).

A



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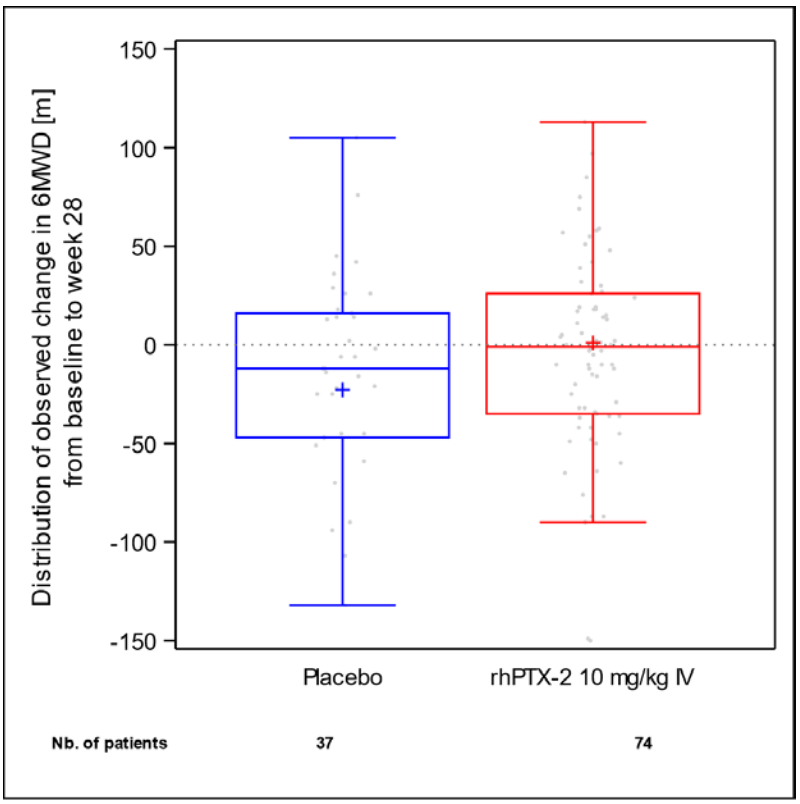

IPF, idiopathic pulmonary fibrosis; rhPTX-2, recombinant human pentraxin-2.

eTable 1. Categorical Changes in FVC Percentage of Predicted Value[a]

Parameter	Total rhPTX-2 (n=67)[b]	Total Placebo (n=35)[c]	No Background Therapy (n=21)[d]		Pirfenidone or Nintedanib (n=81)[e]	
			rhPTX-2 (n=13)[f]	Placebo (n=8)[g]	rhPTX-2 (n=54)[h]	Placebo (n=27)[i]
	n (%)					
Increase in FVC percentage of predicted value ≥5% or ≥100 mL						
≥5%	2 (3)	0	1 (8)	0	1 (2)	0
≥10%	0	0	0	0	0	0
≥100 mL	7 (10)	0	1 (8)	0	6 (11)	0
≥200 mL	0	0	0	0	0	0
Decrease or increase in FVC percentage of predicted value <5%						
Change <5%	45 (67)	22 (63)	10 (77)	6 (75)	35 (65)	16 (59)
Decline in FVC percentage of predicted value (changes ≥5% or ≥100 mL)						
≥5%	20 (30)	13 (37)	2 (15)	2 (25)	18 (33)	11 (41)
≥10%	2 (3)	3 (9)	1 (8)	0	1 (2)	3 (11)
≥100 mL	37 (55)	18 (51)	5 (38)	2 (25)	32 (59)	16 (59)
≥200 mL	21 (31)	9 (26)	2 (15)	1 (13)	19 (35)	8 (30)

[a]N corresponds to the number of patients evaluated.

[b]Data are missing for 10 patients.

[c]Data are missing for 4 patients.

[d]Data are missing for 4 patients.

[e]Data are missing for 10 patients.

[f]Data are missing for 3 patients.

[g]Data are missing for 1 patient.

[h]Data are missing for 7 patients.

[i]Data are missing for 3 patients.

eTable 2. Adverse Events[a]

Event	rhPTX-2 (n=77)	Placebo (n=39)
	n (%)	
Any adverse event	71 (92)	36 (92)
Most frequent adverse events[b]		
Cough	14 (18)	2 (5)
Fatigue	13 (17)	4 (10)
Nasopharyngitis	12 (16)	9 (23)
Headache	11 (14)	3 (8)
Idiopathic pulmonary fibrosis	11 (14)	5 (13)
Diarrhea	9 (12)	2 (5)
Bronchitis	8 (10)	5 (13)
Dyspnea	7 (9)	4 (10)
Upper respiratory tract infection	7 (9)	5 (13)
Dizziness	6 (8)	3 (8)
Dyspnea exertional	5 (6)	0
Nausea	5 (6)	2 (5)
Decreased appetite	4 (5)	2 (5)
Hypoxia	4 (5)	0
Pain in extremity	4 (5)	3 (8)
Respiratory tract infection	4 (5)	2 (5)
Arthralgia	3 (4)	2 (5)
Back pain	3 (4)	4 (10)

Influenza	**3 (4)**	**3 (8)**
Influenza-like illness	**3 (4)**	**2 (5)**
Productive cough	**3 (4)**	**3 (8)**
Sinusitis	**3 (4)**	**3 (8)**
Anemia	**2 (3)**	**2 (5)**
Epistaxis	**2 (3)**	**2 (5)**
Wheezing	**2 (3)**	**2 (5)**
Hypokalemia	**1 (1)**	**2 (5)**
Oropharyngeal pain	**1 (1)**	**2 (5)**
Pneumonia	**1 (1)**	**2 (5)**
Aspartate aminotransferase increased	**0**	**3 (8)**
Depression	**0**	**2 (5)**
Severe adverse events[c]	**7 (9)**	**2 (5)**
Serious adverse events[d]	**6 (8)**	**4 (10)**
Fatal adverse events	**0**	**1 (3)**
Adverse events leading to study drug discontinuation	**2 (3)**	**1 (3)**
Pneumonia	**0**	**1 (3)**
Lung carcinoma cell type unspecified stage II	**1 (1)**	**0**
Idiopathic pulmonary fibrosis	**1 (1)**	**0**

[a] Events occurring after the patient received treatment.

[b] The most frequent adverse events were defined as those with an incidence of >5% in any study group ordered by frequency of occurrence in the rhPTX-2 group.

[c] Adverse events were graded as follows: Grade 1 (mild), asymptomatic or mild symptoms; clinical or diagnostic observations only; Grade 2 (moderate), minimal, local or noninvasive intervention indicated; Grade 3 (severe), medically significant but not immediately life-threatening; Grade 4 (life-threatening), life-threatening consequences with urgent intervention indicated; and Grade 5 (fatal), death related to adverse event.

[d] A serious adverse event was defined as any adverse event that resulted in death, was immediately life-threatening, resulted in persistent or clinically significant disability or incapacity, required or prolonged hospitalization, was related to a congenital anomaly or birth defect, or was deemed serious for any other reason.