

Supplemental materials

Table S1. Baseline Characteristics, PVR <4 WU and ≥4 WU

	PVR <4 WU				PVR ≥4 WU			
	RCT iTre n=32	RCT PBO n=34	OLE iTre→iTre n=27	OLE PBO→ iTre n=26	RCT iTre n=131	RCT PBO n=129	OLE iTre→iTre n=92	OLE PBO→ iTre n=95
Age, years, mean (SD)	63.8 (11.9)	68.0 (9.8)	63.0 (11.9)	67.6 (10.3)	65.9 (12.9)	67.2 (11.6)	66.6 (13.2)	68.2 (11.5)
<65 years, n (%)	16 (50.0)	10 (29.4)	15 (55.6)	8 (30.8)	49 (37.4)	38 (29.5)	31 (33.7)	25 (26.3)
≥65 years, n (%)	16 (50.0)	24 (70.6)	12 (44.4)	18 (69.2)	82 (62.6)	91 (70.5)	61 (66.3)	70 (73.7)
Sex, n (%)								
Female	13 (40.6)	14 (41.2)	12 (44.4)	10 (38.5)	72 (55.0)	54 (41.9)	51 (55.4)	42 (44.2)
Male	19 (59.4)	20 (58.8)	15 (55.6)	16 (61.5)	59 (45.0)	75 (58.1)	41 (44.6)	53 (55.8)
Ethnicity, n (%)								
Hispanic or Latino	3 (9.4)	0	3 (11.1)	0	8 (6.1)	16 (12.4)	4 (4.3)	10 (10.5)
Not Hispanic or Latino	29 (90.6)	34 (100.0)	24 (88.9)	26 (100.0)	123 (93.9)	112 (86.8)	88 (95.7)	84 (88.4)
Race, n (%)								
White	20 (62.5)	27 (79.4)	16 (59.3)	22 (84.6)	92 (70.2)	99 (76.7)	62 (67.4)	76 (80.0)
Black or African American	9 (28.1)	6 (17.6)	8 (29.6)	4 (15.4)	32 (24.4)	24 (18.6)	25 (27.2)	16 (16.8)
American Indian or Alaskan Native	1 (3.1)	0	1 (3.7)	0	1 (0.8)	1 (0.8)	1 (1.1)	1 (1.1)
Asian	2 (6.3)	1 (2.9)	2 (7.4)	0	5 (3.8)	4 (3.1)	4 (4.3)	2 (2.1)
Weight (kg), mean (SD)	92.7 (18.8)	92.9 (24.0)	90.01 (18.9)	95.7 (23.6)	81.7 (20.4)	81.0 (18.9)	81.6 (21.5)	82.1 (18.9)
BMI (kg/m ²), mean (SD)	31.5 (5.2)	31.5 (6.3)	31.0 (5.7)	32.5 (5.7)	29.6 (6.9)	28.3 (5.6)	29.5 (7.2)	28.9 (5.7)
6MWD (m), mean (SD)	297.2 (110.1)	297.7 (91.8)	302.7 (108.8)	327.7 (104.8)	243.5 (98.0)	256.5 (91.9)	275.3 (96.4)	250.6 (110.4)
NT-proBNP (pg/mL), mean (SD)	461.9 (652.6)	737.7 (1535.1)	309.7 (362.8)	364.3 (513.2)	2203.6 (3461.5)	2087.2 (3398.3)	1613.8 (2474.0)	3868.2 (10561.4)
PVR (WU), mean (SD)	3.6 (0.2)	3.5 (0.3)	3.6 (0.2)	3.5 (0.3)	7.1 (2.8)	6.7 (2.7)	6.9 (2.8)	6.4 (2.5)
mPAP (mmHg), mean (SD)	31.1 (4.4)	30.4 (4.5)	31.4 (4.7)	30.7 (4.9)	38.7 (8.7)	37.4 (8.6)	39.1 (9.3)	36.6 (8.2)
PCWP (mmHg), mean (SD)	10.8 (3.2)	11.0 (2.9)	10.8 (3.3)	10.7 (3.1)	9.9 (3.5)	9.2 (3.5)	9.9 (3.6)	9.3 (3.4)
Time since diagnosis (years), mean (SD)	0.42 (0.58)	1.03 (2.33)	0.73 (0.62)	1.48 (2.63)	0.57 (1.26)	0.41 (0.83)	0.93 (1.26)	0.76 (0.95)
Current ILD Diagnosis, n (%)								
IIP	14 (43.8)	19 (55.9)	12 (44.4)	14 (53.8)	51 (38.9)	62 (48.1)	35 (38.0)	47 (49.5)
CHP	0	1 (2.9)	0	1 (3.8)	10 (7.6)	8 (6.2)	7 (7.6)	5 (5.3)
Occupational lung disease	0	0	0	0	5 (3.8)	1 (0.8)	3 (3.3)	1 (1.1)

CPFE	8 (25.0)	9 (26.5)	6 (22.2)	7 (26.9)	34 (26.0)	31 (24.0)	23 (25.0)	22 (23.2)
CTD	10 (31.3)	5 (14.7)	9 (33.3)	4 (15.4)	30 (22.9)	27 (20.9)	24 (26.1)	20 (21.1)
Other	0	0	0	0	1 (0.8)	0	0	0

6MWD, 6-minute walk distance; BMI, body mass index; CHP, chronic hypersensitivity pneumonia; CPFE, combined pulmonary fibrosis and emphysema; CTD, connective tissue disorder; IIP, idiopathic interstitial pneumonia; iTre, inhaled treprostinil; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OLE; open-label extension; mPAP, mean pulmonary artery pressure; PBO, placebo; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RCT, randomized controlled trial; WU, Wood unit

Table S2. Baseline Demographics, PVR ≤5 WU and >5 WU

	≤5 WU				>5 WU			
	RCT iTre n=69	RCT PBO n=81	OLE iTre→iTre n=55	OLE PBO→ iTre n=64	RCT iTre n=94	RCT PBO n=82	OLE iTre→iTre n=64	OLE PBO→ iTre n=57
Age, years, mean (SD)	65.9 (11.3)	67.9 (10.6)	66.2 (10.9)	68.3 (10.9)	65.3 (13.7)	66.9 (11.8)	65.4 (14.6)	67.8 (11.6)
<65 years, n (%)	29 (42.0)	23 (28.4)	22 (40.0)	18 (28.1)	36 (38.3)	25 (30.5)	24 (37.5)	15 (26.3)
≥65 years, n (%)	40 (58.0)	58 (71.6)	33 (60.0)	46 (71.8)	58 (61.7)	57 (69.5)	40 (62.5)	42 (73.7)
Sex, n (%)								
Female	29 (42.0)	35 (43.2)	23 (41.8)	27 (42.2)	56 (59.6)	33 (40.2)	40 (62.5)	25 (43.9)
Male	40 (58.0)	46 (56.8)	32 (58.2)	37 (57.8)	38 (40.4)	49 (59.8)	24 (37.5)	32 (56.1)
Ethnicity, n (%)								
Hispanic or Latino	3 (4.3)	6 (7.4)	3 (5.5)	3 (4.7)	8 (8.5)	10 (12.2)	4 (6.3)	7 (12.3)
Not Hispanic or Latino	66 (95.7)	75 (92.6)	52 (94.5)	61 (95.3)	86 (91.5)	71 (86.6)	60 (93.8)	49 (86.0)
Missing	0	0	0	0	0	1 (1.2)	0	1 (1.8)
Race, n (%)								
White	46 (66.7)	66 (81.5)	36 (65.5)	54 (84.4)	66 (70.2)	60 (73.2)	42 (65.6)	44 (77.2)
Black or African American	16 (23.2)	13 (16.0)	13 (23.6)	10 (15.6)	25 (26.6)	17 (20.7)	20 (31.3)	10 (17.5)
American Indian or Alaskan Native	2 (2.9)	0	2 (3.6)	0	0	1 (1.2)	0	1 (1.8)
Asian	5 (7.2)	1 (1.2)	4 (7.3)	0	2 (2.1)	4 (4.9)	2 (3.1)	2 (3.5)
Missing	0	1 (1.2)	0	0	1 (1.1)	0	0	0
Weight (kg), mean (SD)	91.5 (20.6)	89.3 (22.2)	91.1 (20.8)	91.3 (21.2)	78.3 (18.7)	77.8 (17.2)	77.1 (19.8)	78.1 (17.9)
Height (cm), mean (SD)	170.4 (10.7)	170.0 (9.6)	170.5 (11.0)	170.3 (10.1)	165.4 (9.6)	167.9 (9.2)	165.3 (9.2)	166.6 (8.9)
BMI (kg/m ²), mean (SD)	31.4 (6.0)	30.5 (6.1)	31.2 (6.0)	31.1 (5.6)	28.9 (6.8)	27.5 (5.3)	28.6 (7.5)	28.1 (5.8)
6MWD (m), mean (SD)	281.0 (105.7)	284.5 (90.7)	291.5 (111.2)	301.1 (106.3)	234.2 (95.6)	246.0 (92.1)	273.2 (88.0)	228.3 (109.0)
NT-proBNP (pg/mL), mean (SD)	758.1 (1207.6)	1117.5 (2156.6)	525.9 (763.6)	1329.4 (3771.6)	2685.2 (3896.0)	2500.2 (3789.3)	2011.0 (2827.6)	5120.3 (12964.7)
PVR (WU), mean (SD)	4.0 (0.5)	4.1 (0.6)	4.0 (0.5)	4.1 (0.6)	8.1 (2.6)	7.9 (2.6)	8.0 (2.6)	7.6 (2.6)
mPAP (mmHg), mean (SD)	32.2 (4.8)	31.7 (5.5)	32.3 (4.8)	31.7 (5.4)	41.0 (8.9)	40.2 (8.6)	41.8 (9.6)	39.3 (8.6)
PCWP (mmHg), mean (SD)	10.6 (3.3)	10.2 (3.0)	10.5 (3.4)	10.2 (3.0)	9.7 (3.5)	8.9 (3.9)	9.8 (3.7)	9.0 (3.7)
Time since diagnosis (years), mean (SD)	0.66 (1.43)	0.65 (1.61)	0.90 (1.23)	1.02 (1.78)	0.46 (0.91)	0.43 (0.92)	0.88 (1.08)	0.80 (1.08)
Current ILD Diagnosis, n (%)								
IIP	29 (42.0)	43 (53.1)	22 (40.0)	35 (54.7)	36 (38.3)	38 (46.3)	25 (39.1)	26 (45.6)

CHP	2 (2.9)	2 (2.5)	2 (3.6)	1 (1.6)	8 (8.5)	7 (8.5)	5 (7.8)	5 (8.8)
Occupational lung disease	2 (2.9)	0	2 (3.6)	0	3 (3.2)	1 (1.2)	1 (1.6)	1 (1.8)
CPFE	16 (23.2)	19 (23.5)	12 (21.8)	14 (21.9)	26 (27.7)	21 (25.6)	17 (26.6)	15 (26.3)
CTD	20 (29.0)	17 (21.0)	17 (30.9)	14 (21.9)	20 (21.3)	15 (18.3)	16 (25.0)	10 (17.5)
Other	0	0	0	0	1 (1.1)	0	0	0

6MWD, 6-minute walk distance; BMI, body mass index; iTre, inhaled treprostinil; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OLE, open-label extension; PBO, placebo; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RCT, randomized controlled trial; WU, Wood unit

Table S3: Clinical worsening events in the INCREASE RCT by PVR

Clinical worsening event, n (%)	PVR <4 WU		PVR ≥4 WU	
	Inhaled treprostinil (n=32)	Placebo (n=34)	Inhaled treprostinil (n=131)	Placebo (n=129)
Any first event	3 (9.4)	8 (23.5)	34 (26.0)	46 (35.7)
Cardiopulmonary hospitalization	0	5 (14.7)	18 (13.7)	19 (14.7)
>15% decrease in 6MWD	3 (9.4)	2 (5.9)	10 (7.6)	24 (18.6)
Lung transplantation	0	0	2 (1.5)	0
Death	0	1 (2.9)	4 (3.1)	3 (2.3)
Clinical worsening event, n (%)	PVR ≤5 WU		PVR >5 WU	
	Inhaled treprostinil (n=69)	Placebo (n=81)	Inhaled treprostinil (n=32)	Placebo (n=34)
Any first event	13 (18.8)	20 (24.7)	24 (25.5)	34 (41.5)
Cardiopulmonary hospitalization	5 (7.2)	10 (12.3)	13 (13.8)	14 (17.1)
>15% decrease in 6MWD	6 (8.7)	8 (9.9)	7 (7.4)	18 (22.0)
Lung transplantation	1 (1.4)	0	1 (1.1)	0
Death	1 (1.4)	2 (2.5)	3 (3.2)	2 (2.4)

6MWD, 6-minute walking distance; PVR, pulmonary vascular resistance; RCT, randomized controlled trial; WU, Wood units

Table S4: Clinical worsening or lung disease exacerbation events in the INCREASE RCT by mPAP

Clinical worsening or exacerbation event, n (%)	mPAP <35 mmHg		mPAP ≥35 mmHg	
	Inhaled treprostinil (n=74)	Placebo (n=80)	Inhaled treprostinil (n=89)	Placebo (n=83)
Any first event	23 (31.1)	39 (48.8)	36 (40.4)	40 (48.2)
Cardiopulmonary hospitalization	3 (4.1)	1 (1.3)	2 (2.2)	3 (3.6)
>15% decrease in 6MWD	3 (4.1)	5 (6.3)	4 (4.5)	8 (9.6)
Lung transplantation	1 (1.4)	0	1 (1.1)	0
Death	2 (2.7)	1 (1.3)	2 (2.2)	2 (2.4)
Exacerbation of underlying lung disease	14 (18.9)	32 (40)	27 (30.3)	27 (32.5)

6MWD, 6-minute walking distance; mPAP, mean pulmonary arterial pressure; RCT, randomized controlled trial

Table S5. Post hoc Bayesian analysis of the phase 3 INCREASE trial for clinical worsening

Prior	Prior median HR	Posterior median HR (95% credible interval)	Probability HR <1	Probability HR <0.8
PVR <4 WU				
Noninformative	N/A	0.34 (0.07, 1.24)	94.81%	89.94%
Optimistic	0.67	0.64 (0.44, 0.92)	99.15%	88.60%
Neutral	1	0.75 (0.39, 1.45)	80.47%	57.40%
Pessimistic	1.3	1.16 (0.79, 1.68)	22.61%	2.66%
PVR ≤5 WU				
Noninformative	N/A	0.66 (0.31, 1.33)	87.75%	70.69%
Optimistic	0.67	0.67 (0.47, 0.94)	98.99%	85.03%
Neutral	1	0.79 (0.47, 1.34)	80.65%	51.08%
Pessimistic	1.3	1.10 (0.79, 1.56)	28.31%	3.19%

HR, hazard ratio; N/A, not applicable; PVR, pulmonary vascular resistance; WU, Wood unit

Table S6. Post hoc Bayesian analysis of the phase 3 INCREASE trial for lung disease exacerbations

Prior	Prior median HR	Posterior median HR (95% credible interval)	Probability HR <1	Probability HR <0.8
PVR <4 WU				
Noninformative	N/A	0.54 (0.18, 1.44)	88.72%	77.97%
Optimistic	0.67	0.65 (0.45, 0.94)	98.93%	86.22%
Neutral	1	0.79 (0.43, 1.45)	77.45%	51.25%
Pessimistic	1.3	1.15 (0.80, 1.65)	22.53%	2.53%
PVR ≤5 WU				
Noninformative	N/A	0.42 (0.22, 0.78)	99.67%	97.86%
Optimistic	0.67	0.59 (0.42, 0.82)	99.95%	96.63%
Neutral	1	0.59 (0.36, 0.95)	98.52%	89.46%
Pessimistic	1.3	0.93 (0.67, 1.29)	66.33%	17.88%

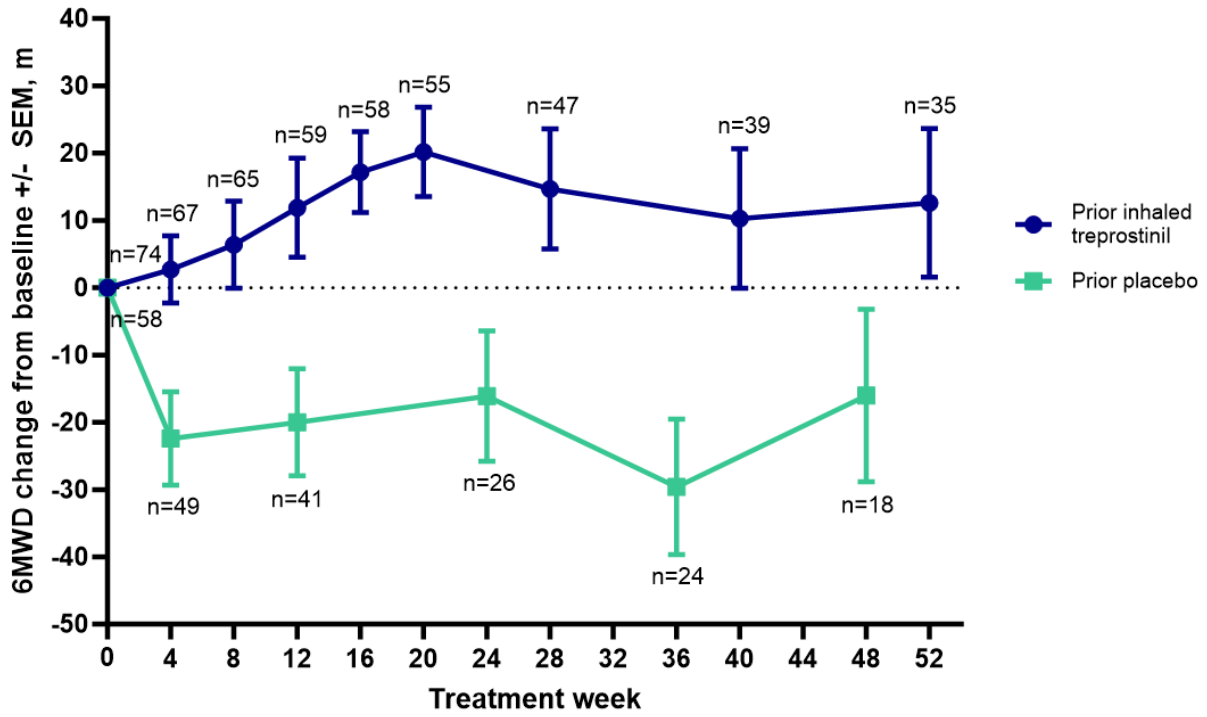
HR, hazard ratio; N/A, not applicable; PVR, pulmonary vascular resistance; WU, Wood unit

Table S7. Clinical events in the INCREASE OLE by Baseline PVR

Clinical event	Hazard ratio (95% CI) for early treatment	
	PVR <4 WU	PVR ≥4 WU
Cardiopulmonary hospitalization	0.46 (0.17, 1.24); <i>P</i> = 0.11	1.07 (0.64, 1.78); <i>P</i> = 0.80
Lung disease exacerbation	0.77 (0.35, 1.7); <i>P</i> = 0.51	0.68 (0.46, 1.0); <i>P</i> = 0.04
Death	0.62 (0.15, 2.49); <i>P</i> = 0.49	0.7 (0.41, 1.19), <i>P</i> = 0.19
Clinical event		
	PVR ≤5 WU	PVR >5 WU
Cardiopulmonary hospitalization	0.81 (0.39, 1.68); <i>P</i> = 0.57	0.95 (0.53, 1.70); <i>P</i> = 0.87
Lung disease exacerbation	0.55 (0.33, 0.93); <i>P</i> = 0.02	0.84 (0.52, 1.33), <i>P</i> = 0.45
Death	0.50 (0.21, 1.21); <i>P</i> = 0.12	0.77 (0.42, 1.43); <i>P</i> = 0.41

CI, confidence interval; OLE, open-label extension; PVR, pulmonary vascular resistance; WU, Wood unit

Figure S1: 6MWD change in the INCREASE OLE, mPAP <35 mmHg



6MWD, 6-minute walking distance; mPAP, mean pulmonary arterial pressure; OLE, open-label extension, SEM, standard error of measurement