

# Improvement in HRCT lung fibrosis with inhaled pirfenidone is associated with better health-related quality of life scores in patients with idiopathic pulmonary fibrosis

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## OBJECTIVES

AP01 is a novel formulation of inhaled pirfenidone[1] with potentially improved efficacy and reduced toxicity compared to oral pirfenidone in Idiopathic Pulmonary Fibrosis (IPF).

Computer-assisted quantification of the serial change in Quantitative Lung Fibrosis ( $\delta QLF$ ) on thoracic High-Resolution Computed Tomography (HRCT) correlates with changes in FVC and mortality. Correlation of longitudinal changes in quality of life (QOL) and  $\delta QLF$  are less established.

AP01-002 was a Phase 1b trial comparing the safety and tolerability of two regimes of AP01, 50mg once daily (qd) and 100mg twice daily (bid) in IPF.

## METHODS

91 patients were randomized to receive AP01 50 mg qd or 100 mg bid. HRCTs were performed at baseline and 24 weeks, reviewed for image quality and quantitatively scored (representative patient shown in Figure 1)

Forced Vital Capacity (FVC), and QOL measures, including the King's Brief Interstitial Lung Disease (KBILD) questionnaire were collected every 4 weeks until 24 weeks and every 12 weeks until 72 weeks thereafter. KBILD Minimal Clinically Important Difference (MCID) for total score is 5 points [2]. QLF improvement is defined as a greater than 2% reduction in QLF score from baseline to 24 weeks [3]. Stable is defined as QLF score change between -2% and 2% and worsening is defined as a greater than 2% increase in QLF score.

## RESULTS

- 69 patients underwent baseline and week 24 HRCT scans with appropriate image quality for analysis (Table 1)
- Mean FVC change at 48 weeks -185 mL for 50 mg qd and -46 mL for 100 mg bid (Table 2)
  - Slope at 48 weeks -187 mL for 50 mg qd and -57 mL for 100 mg bid
- Higher % of patients had stable or improved QLF score in 100 mg bid group (Figure 2)
- $\delta QLF$  and change in FVC showed stronger correlation in 100 mg bid (Figure 3)
- Patients with improved QLF had higher average change in KBILD Total, Breathlessness & Activities, and Psychological scores (Figure 4)
  - Apparent from week 8 and maintained until week 48 in 100 mg bid

Table 1. Characteristics of patients with a baseline and week 24 HRCT scan

Characteristic	50 mg qd (N=38)	100 mg bid (N=31)	Total (N=69)
<b>Region, n (%)</b>			
Asia Pacific	20 (52.6)	16 (51.6)	36 (52.2)
Europe	18 (47.4)	15 (48.4)	33 (47.8)
<b>Age at screening (years), mean (SD)</b>	73.4 (6.99)	70.7 (8.49)	72.2 (7.77)
<b>Male, n (%)</b>	28 (73.7)	24 (77.4)	52 (75.4)
<b>White Race, n (%)</b>	37 (97.4)	29 (93.5)	66 (95.7)
<b>Former smoker, n (%)</b>	27 (71.1)	22 (71.0)	49 (71.0)
<b>Pulmonary function testing</b>			
<b>FVC % predicted at screening <math>\geq</math>50% predicted, n (%)</b>	35 (92.1)	31 (100.0)	66 (95.7)
<b>FVC at baseline, mean (SD)</b>			
L	2.5 (0.59)	2.7 (0.64)	2.6 (0.62)
% predicted	69.8 (12.04)	73.2 (9.03)	71.3 (10.85)
<b>FEV<sub>1</sub> % predicted at baseline, mean (SD)</b>	76.2 (12.65)	77.4 (9.80)	76.8 (11.39)
<b>D<sub>100</sub> % predicted at baseline (mL/min/mm Hg), mean (SD)</b>	47.2 (13.36)	48.3 (11.01)	47.7 (12.28)
<b>HRCT</b>			
<b>Pattern, n (%)</b>			
Typical UIP	14 (36.8)	17 (54.8)	31 (44.9)
Probable UIP	23 (60.5)	12 (38.7)	35 (50.7)
Indeterminate UIP	1 (2.6)	2 (6.5)	3 (4.3)
<b>QLF at baseline, mean (SD)</b>			
mL of whole lung	645.6 (307.52)	478.7 (304.25)	570.6 (315.10)
% of whole lung	18.4 (11.02)	11.9 (7.89)	15.5 (10.21)
<b>Ground glass at baseline, mean (SD)</b>			
mL of whole lung	729.9 (311.68)	727.4 (258.60)	728.8 (286.99)
% of whole lung	19.2 (6.53)	17.7 (6.10)	18.6 (6.34)
<b>Honeycomb at baseline, mean (SD)</b>			
mL of whole lung	22.7 (31.16)	20.2 (21.94)	21.6 (27.24)
% of whole lung	0.6 (0.89)	0.5 (0.56)	0.6 (0.76)
<b>Total Lung Capacity (L), mean (SD)</b>	3.8 (0.90)	4.2 (0.89)	4 (0.91)
<b>KBILD score at baseline, mean (SD)</b>			
Total	53.8 (13.54)	56.5 (11.82)	55.0 (12.78)
Breathlessness and activities	40.6 (16.97)	43.0 (19.94)	41.7 (18.27)
Chest symptoms	64.7 (23.73)	69.8 (21.57)	67.0 (22.76)
Psychological	53.8 (18.50)	57.7 (15.93)	55.6 (17.37)

Table 2. Absolute and change from baseline for whole lung HRCT parameters and FVC

Parameter, mean (SD)	50 mg qd (N=38)	100 mg bid (N=31)	Total (N=69)
<b>QLF</b>			
mL			
Week 24	665.9 (331.29)	483.3 (317.36)	583.9 (335.45)
Change from baseline	20.3 (171.24)	4.6 (160.58)	13.3 (165.51)
%			
Week 24	19.3 (11.69)	12.4 (9.23)	16.2 (11.14)
Change from baseline	1.0 (6.15)	0.5 (4.55)	0.7 (5.46)
<b>Ground glass</b>			
mL			
Week 24	710.3 (298.61)	680.2 (245.57)	696.8 (274.50)
Change from baseline	-19.6 (112.24)	-47.2 (127.15)	-32.0 (119.07)
%			
Week 24	19.5 (7.04)	16.9 (6.66)	18.3 (6.94)
Change from baseline	0.2 (4.49)	-0.8 (4.14)	-0.2 (4.33)
<b>Honeycomb</b>			
mL			
Week 24	18.4 (24.10)	28.6 (52.06)	23.0 (39.21)
Change from baseline	-4.3 (21.94)	8.3 (41.67)	1.4 (32.68)
%			
Week 24	0.5 (0.68)	0.6 (0.96)	0.6 (0.81)
Change from baseline	-0.1 (0.59)	0.1 (0.90)	0.0 (0.75)
<b>Total Lung Capacity</b>			
Week 24 (L)	3.7 (0.85)	4.2 (0.98)	3.9 (0.93)
Change from baseline at week 24 (mL)	-114.2 (480.05)	-44.0 (326.51)	-82.7 (416.72)
<b>FVC</b>			
Week 24 (L)	2.4 (0.65)	2.7 (0.70)	2.5 (0.68)
Change from baseline at week 24 (mL)	-76.1 (185.28)	0.6 (271.17)	-41.6 (229.34)
Week 48 (L)	2.3 (0.64)	2.7 (0.70)	2.5 (0.69)
Change from baseline at week 48 (mL)	-184.5 (207.27)	-46.1 (298.46)	-122.3 (259.77)
<b>FVC % predicted</b>			
Week 24	68.0 (14.06)	73.7 (12.58)	70.6 (13.63)
Change from baseline at week 24	-1.8 (5.39)	0.5 (7.12)	-0.7 (6.29)
Week 48	65.2 (13.76)	72.7 (13.52)	68.6 (14.07)
Change from baseline at week 48	-4.6 (6.02)	-0.4 (7.87)	-2.7 (7.17)

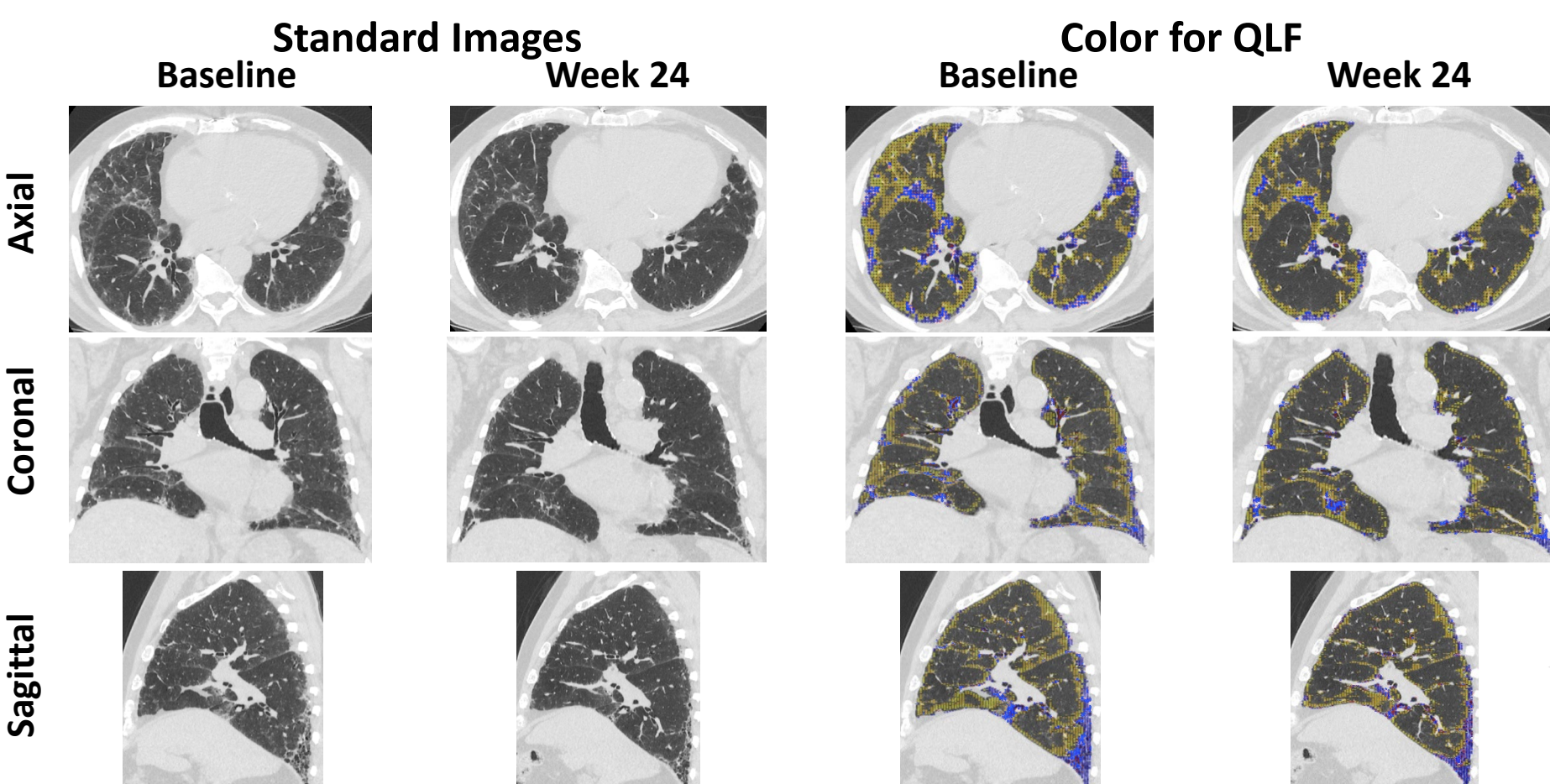


Figure 1. Baseline and week 24 images of a 100 mg bid patient showing improved QLF and FVC

	Baseline	Week 24
<b>Total Lung Capacity</b>	<b>3.95 L</b>	<b>4.09 L</b>
<b>QLF (%)</b>	<b>15.2%</b>	<b>11.0%</b>
<b>QLF (mL)</b>	<b>600 mL</b>	<b>449 mL</b>
<b>FVC % Predicted</b>	<b>64%</b>	<b>77%</b>
<b>FVC (L)</b>	<b>2.41 L</b>	<b>2.91 L</b>

Figure 2. Waterfall plot of change in QLF (% of whole lung) at week 24

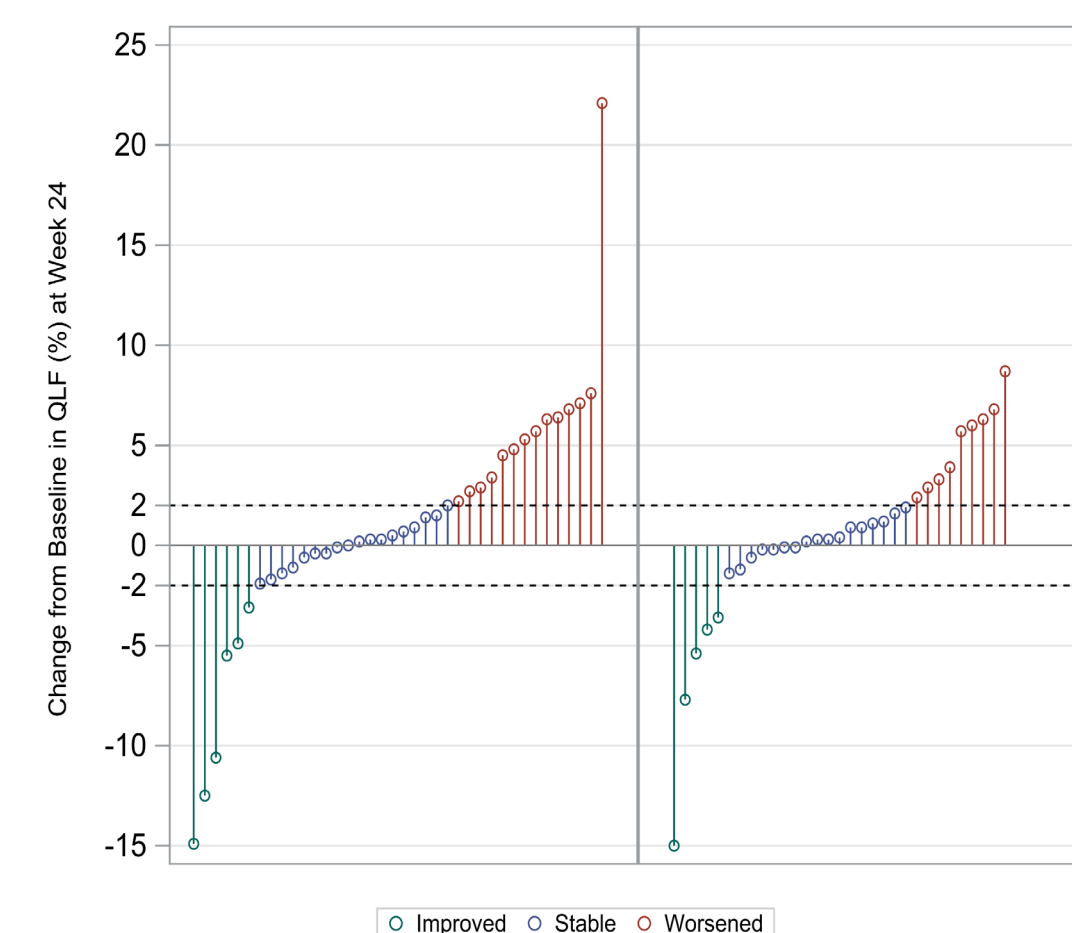


Figure 3. Correlation between change from baseline in QLF (mL) and FVC (mL)

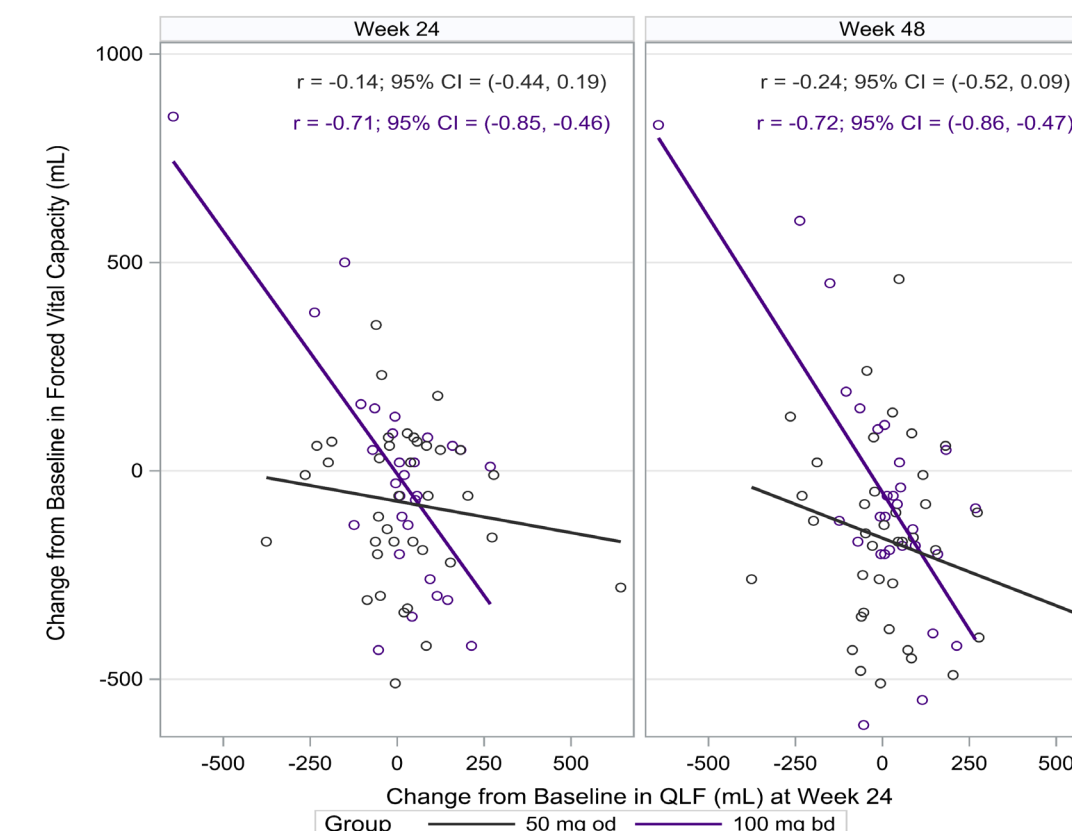
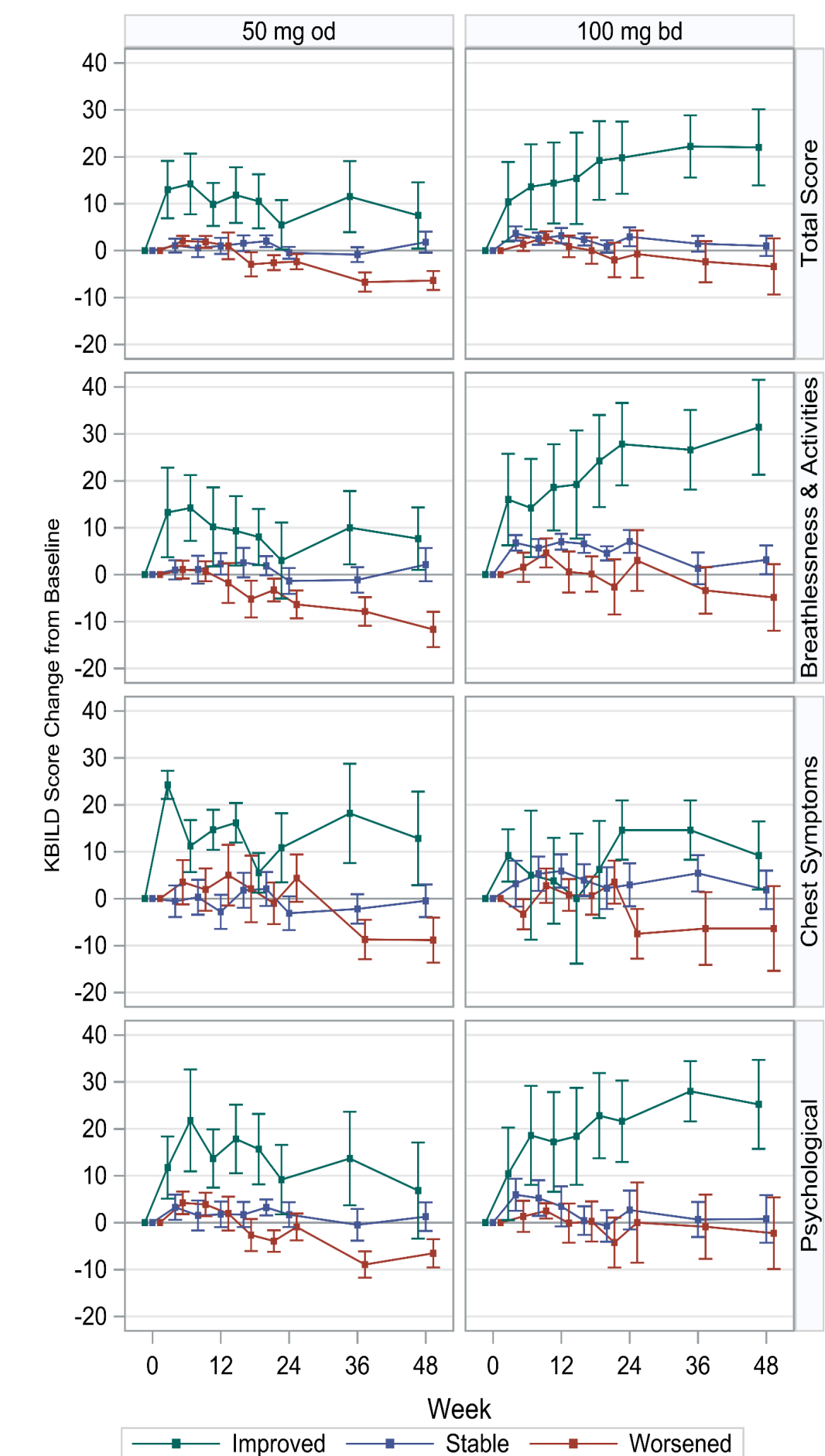


Figure 4. Mean change from baseline in the KBILD questionnaire by category of change in QLF (% of whole lung)



## CONCLUSION

This study shows a strong and lasting association between CT response and KBILD, a validated and meaningful study endpoint.

- Khoo JK et al. A randomized, double-blinded, placebo-controlled, dose-escalation phase 1 study of aerosolized pirfenidone delivered via the PARI investigational eFlow nebulizer in volunteers and patients with idiopathic pulmonary fibrosis. J Aerosol Med Pulm Drug Deliv. 2020 Feb;33(1):15-20.
- Sinha A et al. The King's Brief Interstitial Lung Disease (KBILD) questionnaire: an updated minimal clinically important difference. BMJ Open Respiratory Research 2019;6:e000363.
- Kim GHJ et al. Prediction of idiopathic pulmonary fibrosis progression using early quantitative changes on CT imaging for a short term of clinical 18-24-month follow-ups. Eur Radiol. 2020 Feb;30(2):726-734.