Supplementary Appendix

Supplementary Table S1. Baseline characteristics and haemodynamics among patients with SSc-PAH and non-SSc-CTD

	Combination Therapy (SSc) (n=71)	Monotherapy Pooled (SSc) (n=47)	Combination Therapy (non-SSc CTD) (n=32)	Monotherapy Pooled (non-SSc CTD) (n=37)
Median (Q1, Q3) time from diagnosis to study drug administration (days)	20 (8, 45)	16 (8, 35)	23.5 (11.5, 99)	29 (11, 62)
Mean (SD) age (years)	62.0 (9.2)	60.7 (10.7)	50.4 (14.6)	54.4 (15.1)
Sex, n (%)				
Female	58 (82)	41 (87)	31 (97)	35 (95)
Male	13 (18)	6 (13)	1 (3)	2 (5)
WHO functional class, n (%)				
II	16 (23)	11 (23)	10 (31)	11 (30)
III	55 (77)	36 (77)	22 (69)	26 (70)
6-minute walk distance (m)				
Mean (SD)	312.8 (87.7)	328.9 (98.2)	351.4 (77.8)	326.6 (99.0)
Median	313.2	352.0	367.4	328.0
Median (Q1, Q3) NT-proBNP (ng/L)	1713 (332, 3294) n=68	1152 (382, 2576) n=46	772 (456, 2291) n=30	1128 (261, 2050) n=36
Mean (SD) % of predicted normal TLC	89.8 (16.4) n=70	90.0 (18.4)	87.3 (13.9)	86.6 (16.6) n=36
Mean (SD) % of predicted normal FEV_1	86.2 (19.8)	85.9 (17.4)	80.2 (15.7)	75.6 (12.9)

Prior medications, n (%)				
Immunosuppressants	4 (6)	5 (11)	10 (31)	8 (22)
Steroids	10 (14)	7 (15)	8 (25)	10 (27)
Mean (SD) mean right atrial pressure (mm Hg)	7.4 (4.2)	7.6 (4.7)	7.6 (4.3) n=31	7.7 (4.1)
Mean (SD) cardiac index (L/min/m^2)	2.57 (0.60)	2.54 (0.62) n=46	2.51 (0.69)	2.84 (0.83)
Mean (SD) mean pulmonary arterial pressure (mm Hg)	43.7 (10.3)	45.7 (10.1)	43.1 (10.7)	44.4 (9.9)
Mean (SD) pulmonary capillary wedge pressure (mm Hg)	8.3 (3.0)	8.6 (3.3) n=45	8.1 (3.3) n=31	9.7 (3.3)
Mean (SD) pulmonary vascular resistance (dyne·sec/cm^5)	674.7 (267.8)	702.2 (265.3)	666.8 (293.2)	622.5 (244.1)

Post-hoc summary.
CTD=connective tissue disease; FEV_1=forced expiratory volume in 1 second; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PAH=pulmonary arterial hypertension; Q1=quartile 1; Q3=quartile 3; SD=standard deviation; SSc=systemic sclerosis; TLC=total lung capacity; WHO=World Health Organization.

Supplementary Table S2. Number (%) of patients with a ≥15% decrease from baseline in 6MWD at any time through the final assessment visit (primary analysis set) for subjects with ≥1 post-baseline 6MWD

	Combination therapy	Pooled monotherapy
iPAH/hPAH	31/131 (24%)	46/144 (32%)
CTD-PAH	28/99 (28%)	29/81 (36%)
SSc-PAH	21/67 (31%)	20/45 (44%)
Non-SSc-CTD	7/32 (22%)	9/36 (25%)

Post-hoc summary.

6MWD=6-minute walking distance; CTD=connective tissue disease; hPAH=heritable pulmonary arterial hypertension; iPAH=idiopathic pulmonary arterial hypertension; PAH=pulmonary arterial hypertension; SSc=systemic sclerosis.

Supplementary Table S3. Baseline characteristics and haemodynamics among patients with iPAH/hPAH

	Combination Therapy (n=134)	Monotherapy Pooled (n=145)
Median (Q1, Q3) time from diagnosis to study drug administration (days)	21 (8, 46)	22 (11, 55)
Mean (SD) age (years)	52.5 (15.2)	52.9 (15.5)
Sex, n (%)		
Female	92 (69)	109 (75)
Male	42 (31)	36 (25)
WHO functional class, n (%)		
II	40 (30)	46 (32)
III	94 (70)	99 (68)
6-minute walk distance (m)		
Mean (SD)	368.3 (84.8)	358.6 (86.6)
Median	378.9	368.5
Median (Q1, Q3) NT-proBNP (ng/L)	956 (333, 2130) n=123	999 (292, 1701) n=137
Mean (SD) % of predicted normal TLC	97.0 (15.0)	93.3 (16.9) n=140
Mean (SD) % of predicted normal FEV_1	86.1 (16.1)	85.7 (19.2) n=141

Prior medications, n (%)		
Immunosuppressants	2 (1)	3 (2)
Steroids	5 (4)	6 (4)
Mean (SD) mean right atrial pressure (mm Hg)	8.0 (4.5)	8.2 (5.0) n=144
Mean (SD) cardiac index (L/min/m^2)	2.31 (0.64) n=130	2.33 (0.67) n=142
Mean (SD) mean pulmonary arterial pressure (mm Hg)	51.4 (12.3)	51.4 (13.4)
Mean (SD) pulmonary capillary wedge pressure (mm Hg)	8.6 (3.0) n=127	8.9 (3.4) n=136
Mean (SD) pulmonary vascular resistance (dyne·sec/cm^5)	947.9 (554.9)	893.1 (440.7)

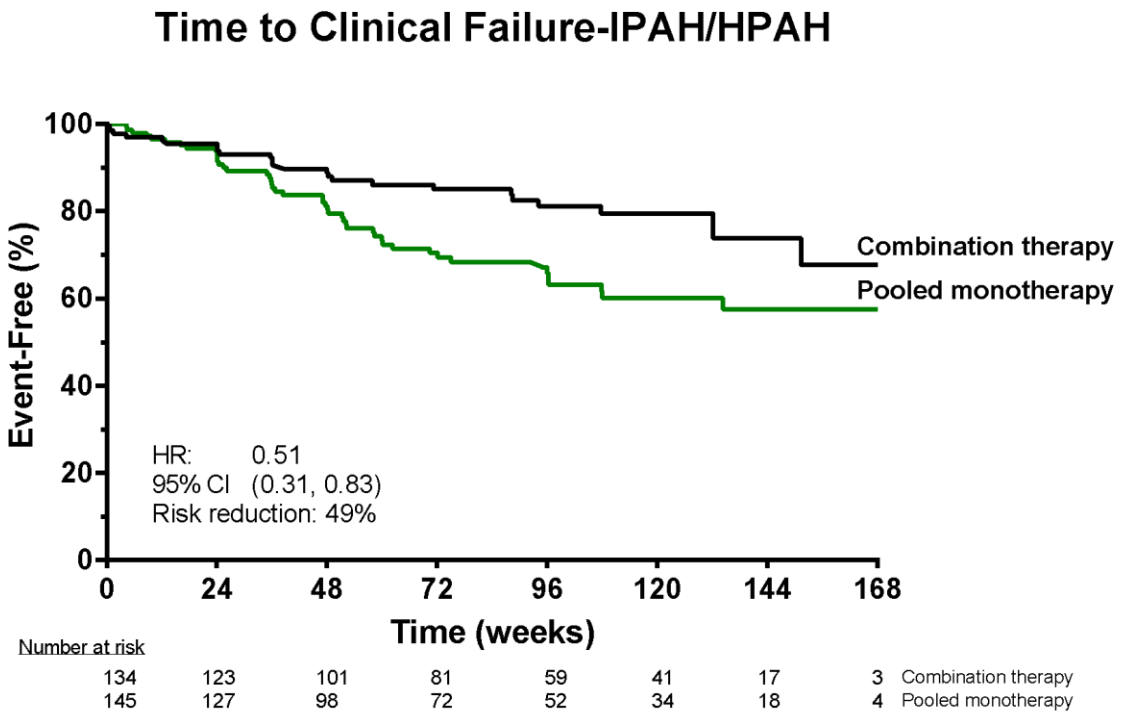
Post-hoc summary.
FEV_1=forced expiratory volume in 1 second; hPAH=heritable pulmonary arterial hypertension; iPAH=idiopathic pulmonary arterial hypertension; NT-proBNP=N-terminal pro-B-type natriuretic peptide; Q1=quartile 1; Q3=quartile 3; SD=standard deviation; TLC=total lung capacity; WHO=World Health Organization.

Supplementary Table S4. Summary of adverse events among patients with iPAH/hPAH

n, (%)	COMB (n=134)	AMB Mono (n=75)	TAD Mono (n=70)
Any AE*	130 (97)	71 (95)	65 (93)
Oedema peripheral	64 (48)	23 (31)	19 (27)
Headache	60 (45)	24 (32)	22 (31)
Diarrhoea	19 (14)	14 (19)	9 (13)
Dyspnoea	20 (15)	13 (17)	10 (14)
Serious AEs†	44 (33)	28 (37)	27 (39)
Pulmonary hypertension‡	4 (3)	8 (11)	3 (4)
Pneumonia	5 (4)	4 (5)	2 (3)
Dyspnoea	4 (3)	0	1 (1)
Anaemia	2 (1)	1 (1)	2 (3)
Syncope	5 (4)	2 (3)	4 (6)
AEs leading to permanent study drug discontinuation§	15 (11)	6 (8)	8 (11)
Oedema peripheral	2 (1)	0	0
Diarrhoea	0	0	0
Nausea	0	0	0
Headache	1 (<1)	0	1 (1)
Dyspnoea	4 (3)	0	1 (1)
Pulmonary oedema	2 (1)	0	0

Post-hoc summary.
*AEs occurring in ≥25% of patients on combination therapy in the iPAH/hPAH population; only the CTD-PAH and/or SSc-PAH populations met this criterion for diarrhoea and dyspnoea (**Table 3** in main text) but rates are shown in this table to allow for comparison.
†SAEs occurring in ≥4% of patients on combination therapy in the iPAH/hPAH population; only the CTD-PAH and/or SSc-PAH populations met this criterion for pulmonary hypertension, pneumonia, dyspnoea, and anaemia (**Table 3** in main text) but rates are shown in this table to allow for comparison. Syncope included after rounding due to clinical importance of event.
‡In each case, the investigator reported the events using additional text not captured in the preferred term, describing this as worsening of pulmonary hypertension. However, an AE report of worsening pulmonary hypertension does not necessarily become a primary endpoint event, which has specific criteria.
§AEs leading to permanent study drug discontinuation in ≥2 patients on combination therapy in the iPAH/hPAH population; only the CTD-PAH and/or SSc-PAH populations met this criterion for diarrhoea, nausea, and headache (**Table 3** in main text) but rates are shown in this table to allow for comparison.
AE=adverse event; AMB=ambrisentan; COMB=combination therapy; CTD=connective tissue disease; hPAH=heritable pulmonary arterial hypertension; iPAH=idiopathic pulmonary arterial hypertension; Mono=monotherapy; PAH=pulmonary arterial hypertension; SAE=serious adverse event; SSc=systemic sclerosis; TAD=tadalafil.

Supplementary Figure S1. Kaplan-Meier curves for time from randomisation to first adjudicated clinical failure in the iPAH/hPAH population

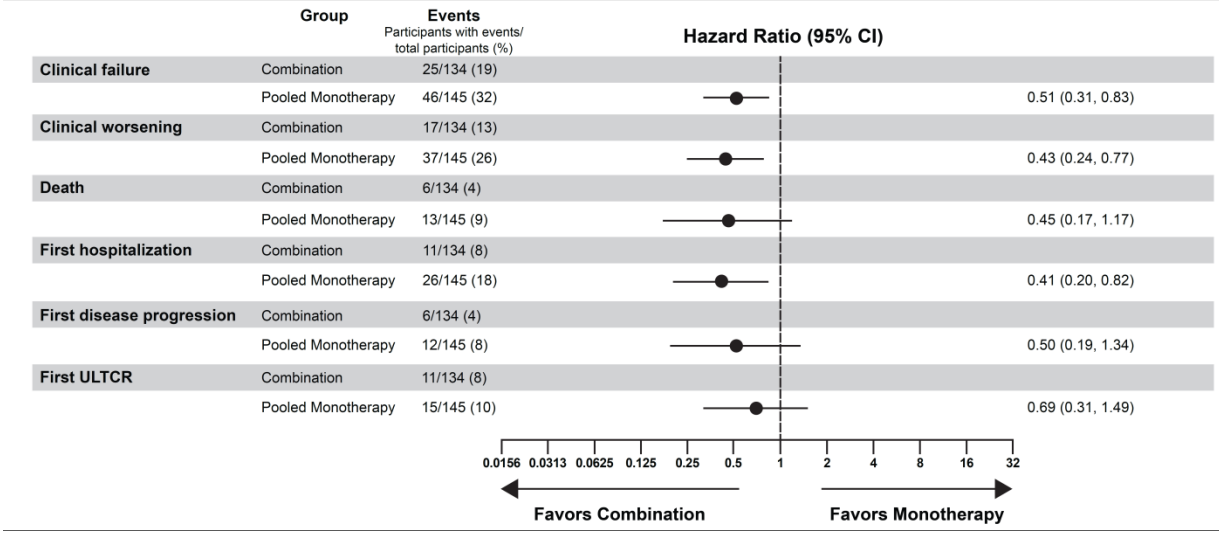


Post-hoc figure.

CI=confidence interval; hPAH=heritable pulmonary arterial hypertension; HR=hazard ratio; iPAH=idiopathic pulmonary arterial hypertension.

HR=hazard ratio for combination versus pooled monotherapy

Supplementary Figure S2. Forest plot of time to first occurrence of clinical failure, clinical worsening, death, hospitalisation, disease progression, and ULTCR in the iPAH/hPAH population



Post-hoc figure.

CI=confidence interval; hPAH=heritable pulmonary arterial hypertension; iPAH=idiopathic pulmonary arterial hypertension; ULTCR=unsatisfactory long-term clinical response.

The hazard ratio is for combination versus pooled monotherapy