Supplementary Material

Methods

Study design

PATENT-1 was a 12-week, randomised, double-blind, placebo-controlled, Phase III trial in which eligible patients were randomly assigned in a 2:4:1 ratio to receive placebo, riociguat individually adjusted up to a maximum of 2.5 mg three times daily (tid) (2.5 mg–maximum group) or riociguat individually adjusted up to 1.5 mg tid (1.5 mg–maximum group; this group was exploratory and not included in efficacy analyses). Details of the riociguat dose-adjustment schedule used in PATENT-1 have been published previously.[15]

PATENT-2 is an open-label, long-term extension study that includes patients who completed PATENT-1 without ongoing study drug-related serious adverse events (SAEs). The study comprises an 8-week, double-blind, dose-adjustment period, followed by an open-label phase that will continue until all patients transition to commercially available riociguat (study ongoing at the time of writing). All patients in PATENT-2 received riociguat individually adjusted up to a maximum of 2.5 mg tid; details of riociguat dose adjustment in PATENT-2 have been published previously.[20]

Patients

Patients with symptomatic pulmonary arterial hypertension (PAH) were included in PATENT-1 if they were aged 18–80 years, had a mean pulmonary artery pressure (mPAP) of ≥25 mm Hg, a pulmonary vascular resistance (PVR) of >300 dyn·s·cm^{-5} and a 6-minute walking distance (6MWD) of 150–450 m. Patients who had received no prior PAH-specific therapies (treatment-naïve) and those who were receiving endothelin receptor antagonists (ERAs) and/or non-intravenous prostanoids at stable doses for ≥90 days were eligible for inclusion, but patients receiving phosphodiesterase type-5 inhibitors were excluded.

Patients in PATENT-1 with PAH-CTD at baseline were identified as having PAH associated with SSc (PAH-SSc) by MedDRA preferred terms ‘scleroderma’, ‘systemic sclerosis’ or ‘CREST syndrome’ in their medical history. Patients with other defined CTD (PAH-other defined CTD) were identified by ‘systemic lupus erythematosus’, ‘systemic lupus erythematosus rash’, ‘rheumatoid arthritis’, ‘mixed connective tissue disease’, ‘undifferentiated connective tissue disease’ or ‘morphea’. All other patients with PAH-CTD were classified as having PAH associated with an unspecified CTD.

Outcome measures

The primary endpoint in PATENT-1 was change in 6MWD from baseline to end of Week 12. Secondary efficacy endpoints included change in PVR, N-terminal pro B-type natriuretic peptide levels, World Health Organization functional class (WHO FC), time to clinical worsening, Borg dyspnoea score and quality of life scores (measured using the EuroQol Group 5-Dimensional Self-report Questionnaire and the Living with Pulmonary Hypertension questionnaire). Safety assessments included adverse events and SAEs, laboratory evaluations, and monitoring of vital signs and echocardiograms throughout the study and safety follow-up period.

The primary aim of PATENT-2 was to assess the safety and tolerability of long-term riociguat and exploratory efficacy assessments including 6MWD and WHO FC.

For 6MWD and WHO FC, missing data due to patient withdrawal or death were imputed at Week 12 of PATENT-1 as previously described; missing data were not imputed for haemodynamic endpoints.

Results

Riociguat 1.5 mg–maximum group

A summary of changes in efficacy endpoints in patients with PAH-CTD in the exploratory riociguat 1.5 mg–maximum group is shown in Supplementary Table 4. Mean±SD 6MWD increased by +7±46 m in the riociguat 1.5 mg–maximum group compared with a decrease of –8±110 m in the placebo group. Fewer patients in the riociguat 1.5 mg–maximum group worsened in WHO FC versus placebo (13% vs 25%), despite patients in the riociguat group having generally worse WHO FC at baseline compared with the placebo group. Haemodynamic changes in patients with PAH-CTD were less pronounced in the riociguat 1.5 mg–maximum group compared with the 2.5 mg–maximum group

Supplementary tables and figures

Supplementary Table 1. Efficacy endpoints for riociguat 2.5 mg–maximum in treatment-naïve and pretreated patients in the PAH-CTD population in PATENT-1.

	Treatment-naïve								Pretreated							
Parameter	**Riociguat 2.5 mg–maximum**				**Placebo**				**Riociguat 2.5 mg–maximum**				**Placebo**			
	n	Baseline	n	Change from baseline at Week 12	n	Baseline	n	Change from baseline at Week 12	n	Baseline	n	Change from baseline at Week 12	n	Baseline	n	Change from baseline at Week 12
6MWD, m	25	361±73	25	21±53	10	339±104	10	38±80	46	341±68	46	17±50	15	375±76	15	–39±118
WHO FC, %	25	I – 8% II – 48% III – 44% IV –0%	25	Improved – 20% Stabilised – 72% Worsened – 8%	10	I – 0% II – 90% III – 10% IV – 0%	10	Improved – 20% Stabilised – 50% Worsened – 30%	46	I – 2% II – 24% III – 72% IV –2%	46	Improved – 24% Stabilised – 76% Worsened – 0%	14	I – 0% II – 43% III – 50% IV –7%	14	Improved – 14% Stabilised – 64% Worsened –21%
PVR, dyn·s·cm^{-5}	25	721±429	24	–259±259	10	584±283	8	–26±253	46	606±297	41	–135±157	15	655±383	12	–45±222
Cardiac index, L/min/m^2	25	2.5±0.7	24	0.6±0.5	10	3.1±0.9	8	–0.2±0.8	46	2.6±0.5	41	0.5±0.6	15	2.7±0.6	12	–0.2±0.5
mPAP, mmHg	25	41.0±11.0	23	–2.2±7.0	10	44.7±16.9	7	–5.9±16.7	46	39.9±9.8	41	–1.4±7.3	15	45.2±16.0	12	–3.8±6.3
RAP, mmHg	25	6.5±5.1	24	2.1±11.5	10	5.8±3.6	8	0.6±7.2	46	7.6±4.0	41	–0.1±4.4	15	6.1±4.0	12	0.7±3.5
PCWP, mmHg	25	8.3±2.7	24	2.5±4.9	10	9.2±2.6	8	–1.6±4.3	46	9.1±3.2	41	2.3±3.2	15	8.7±3.7	12	0.8±4.1

Data are mean±SD unless otherwise indicated.

Missing values, where the patient withdrew or died, were imputed at Week 12 for 6MWD and WHO FC, according to the last observed value, except in cases of death or clinical worsening, when the worst value (0 m) was imputed for 6MWD, and the worst value class (V) was imputed for WHO FC.

6MWD, 6-minute walking distance; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; WHO FC, World Health Organization functional class.

Supplementary Table 2. Efficacy endpoints for riociguat 2.5 mg–maximum in PAH-CTD patients with concomitant immunosuppressant use in PATENT-1.

Parameter	Riociguat 2.5 mg–maximum				Placebo[a]			
	n	Baseline	n	Change from baseline at Week 12	n	Baseline	n	Change from baseline at Week 12
6MWD, m	19	358±78	19	14±63	4	299±105	4	–5±133
WHO FC, %	19	I – 5% II – 11% III – 79% IV – 5%	19	Improved – 32% Stabilised – 68% Worsened – 0%	4	I – 0% II – 50% III – 25% IV – 25%	4	Improved – 25% Stabilised – 77% Worsened – 0%
PVR, dyn·s·cm^{-5}	19	615±343	17	–166±161	4	553±290	3	–172±185
Cardiac index, L/min/m^2	19	2.8±0.7	17	0.6±0.6	4	3.5±0.7	3	–0.2±0.6
mPAP, mmHg	19	41.4±11.3	17	–2.2±5.8	4	44.8±21.8	3	–16.2±16.3
RAP, mmHg	19	6.4±3.4	17	–0.6±4.2	4	4.3±4.3	3	–5.0±2.0
PCWP, mmHg	19	8.9±3.1	17	1.8±2.6	4	8.0±4.1	3	–4.0±4.4

Data are mean±SD unless otherwise indicated.

[a]Due to the low patient numbers in the placebo group, caution should be taken when drawing conclusions about these data.

Missing values, where the patient withdrew or died, were imputed at Week 12 for 6MWD and WHO FC, according to the last observed value, except in cases of death or clinical worsening, when the worst value (0 m) was imputed for 6MWD, and the worst value class (V) was imputed for WHO FC.

6MWD, 6-minute walking distance; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; WHO FC, World Health Organization functional class.

Supplementary Table 3. Efficacy endpoints for riociguat 2.5 mg–maximum in PAH-CTD patients in PATENT-1 who required extra PAH treatment in PATENT-2.

	Riociguat 2.5 mg–maximum				Placebo			
Parameter	**n**	**Baseline**	**n**	**Change from baseline at Week 12**	**n**	**Baseline**	**n**	**Change from baseline at Week 12**
6MWD, m	48	343±69	48	17±45	14	401±54	14	2.2±62
WHO FC, %	48	I – 2% II – 23% III – 75% IV – 0%	48	Improved – 21% Stabilised – 79% Worsened – 0%	13	I – 0% II – 54% III – 39% IV – 8%	13	Improved – 15% Stabilised – 77% Worsened – 8%
PVR, $dyn \cdot s \cdot cm^{-5}$	48	591±238	47	–149±158	14	573±297	14	–16±235
Cardiac index, $L/min/m^2$	48	2.6±0.6	47	0.5±0.5	14	2.8±0.7	14	–0.2±0.6
mPAP, mmHg	48	39.6±9.4	47	–1.8±7.0	14	42.0±13.8	14	–1.7±8.3
RAP, mmHg	48	7.1±4.5	47	0.4±4.7	14	5.2±3.4	14	1.9±4.8
PCWP, mmHg	48	8.6±3.2	47	2.7±3.6	14	8.5±3.7	14	1.1±3.9

Data are mean±SD unless otherwise indicated.

Missing values, where the patient withdrew or died, were imputed at Week 12 for 6MWD and WHO FC, according to the last observed value, except in cases of death or clinical worsening, when the worst value (0 m) was imputed for 6MWD, and the worst value class (V) was imputed for WHO FC.

6MWD, 6-minute walking distance; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; WHO FC, World Health Organization functional class.

Supplementary Table 4. Efficacy endpoints for the overall PAH-CTD group compared with the PAH-CTD group excluding patients with morphea.

	Overall PAH-CTD								PAH-CTD excluding patients with morphea							
	Riociguat 2.5 mg–maximum				Placebo				Riociguat 2.5 mg–maximum				Placebo			
Parameter, mean±SD	n	Baseline	n	Change at Week 12	n	Baseline	n	Change at Week 12	n	Baseline	n	Change at Week 12	n	Baseline	n	Change at Week 12
6MWD, m	71	348±70	71	18±51	25	361±88	25	–8±110	69	347±70	69	19±51	24	358±88	24	–7±112
WHO FC, %	71	I – 4% II – 32% III – 62% IV –1%	71	Improved – 23% Stabilised – 75% Worsened – 3%	24	I – 0% II – 63% III –33% IV – 4%	24	Improved – 17% Stabilised – 58% Worsened – 25%	69	I – 4% II – 33% III – 61% IV –1%	69	Improved – 20% Stabilised – 77% Worsened –3%	23	I – 0% II – 61% III – 35% IV –4%	23	Improved – 17% Stabilised – 61% Worsened – 22%
PVR, dyn·s·cm^{-5}	71	647±350	65	–181±208	25	627±342	20	–37±229	69	655±351	63	–183±210	24	635±347	19	–59±212
Cardiac index, L/min/m^2	71	2.6±0.6	65	0.5±0.5	25	2.9±0.7	20	–0.2±0.6	69	2.6±0.6	63	0.6±0.5	24	2.8±0.7	19	–0.1±0.6
mPAP, mmHg	71	40.3±10.2	64	–1.7±7.1	25	45.0±16.0	19	–4.6±10.9	69	40.5±10.3	62	–1.6±7.2	24	44.8±16.3	18	–5.8±9.8
RAP, mmHg	71	7.2±4.4	65	0.7±7.8	25	6.0±3.8	20	0.7±5.1	69	7.2±4.5	63	0.7±7.8	24	6.2±3.8	19	0.0±4.1
PCWP, mmHg	71	8.8±3.1	65	2.4±3.9	25	8.9±3.3	20	–0.2±4.3	69	8.8±3.0	63	2.2±3.8	24	8.9±3.3	19	–0.4±4.3
NT-proBNP, pg/mL	66	1026±1943	66	274±2576	18	3439±11148	17	54±778	64	1030±1973	64	292±2614	17	3638±11458	16	–8±758
EQ-5D	70	0.69±0.20	70	–0.01±0.24	24	0.66±0.33	24	–0.02±0.40	68	0.69±0.20	68	–0.01±0.25	23	0.66±0.33	23	<–0.01±0.40
LPH	68	41.6±19.9	68	–3.32±19.2	24	42.3±23.7	24	2.01±26.3	67	41.7±20.0	67	–3.1±19.2	23	41.6±23.9	23	1.7±26.9

Data are mean±SD unless otherwise indicated.

Missing values, where the patient withdrew or died, were imputed at Week 12 for 6MWD and WHO FC, according to the last observed value, except in cases of death or clinical worsening, when the worst value (0 m) was imputed for 6MWD, and the worst value class (V) was imputed for WHO FC.

6MWD, 6-minute walking distance; EQ-5D, EuroQol 5 Dimensions questionnaire; LPH, Living with Pulmonary Hypertension questionnaire; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; WHO FC, World Health Organization functional class.

Supplementary Table 5. Efficacy endpoints for riociguat 1.5 mg–maximum in the overall PAH-CTD population in PATENT-1.

Parameter	Riociguat 1.5 mg–maximum				Placebo			
	n	Baseline	n	Change from baseline at Week 12	n	Baseline	n	Change from baseline at Week 12
6MWD, m	15	356±81	15	+7±46	25	361±88	25	–8±110
WHO FC, %	15	I – 13% II – 13% III – 73% IV – 0%	15	Improved – 20% Stabilised – 67% Worsened – 13%	24	I – 0% II – 63% III – 33% IV – 4%	24	Improved – 17% Stabilised – 58% Worsened – 25%
PVR, dyn·s·cm^{-5}	15	545±237	13	–112±79	25	627±342	20	–37±229
Cardiac index, L/min/m^2	15	2.8±0.6	13	0±0.5	25	2.9±0.7	20	–0.2±0.6
mPAP, mmHg	15	41.6±9.1	13	–5.6±4.5	25	45.0±16.0	19	–4.6±10.9
RAP, mmHg	15	7.7±3.4	13	–0.8±4.0	25	6.0±3.8	20	0.7±5.1
PCWP, mmHg	15	10.5±2.4	13	1.2±4.3	25	8.9±3.3	20	–0.2±4.3

Data are mean±SD unless otherwise indicated.

Missing values, where the patient withdrew or died, were imputed at Week 12 for 6MWD and WHO FC, according to the last observed value, except in cases of death or clinical worsening, when the worst value (0 m) was imputed for 6MWD, and the worst value class (V) was imputed for WHO FC.

6MWD, 6-minute walking distance; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; WHO FC, World Health Organization functional class.

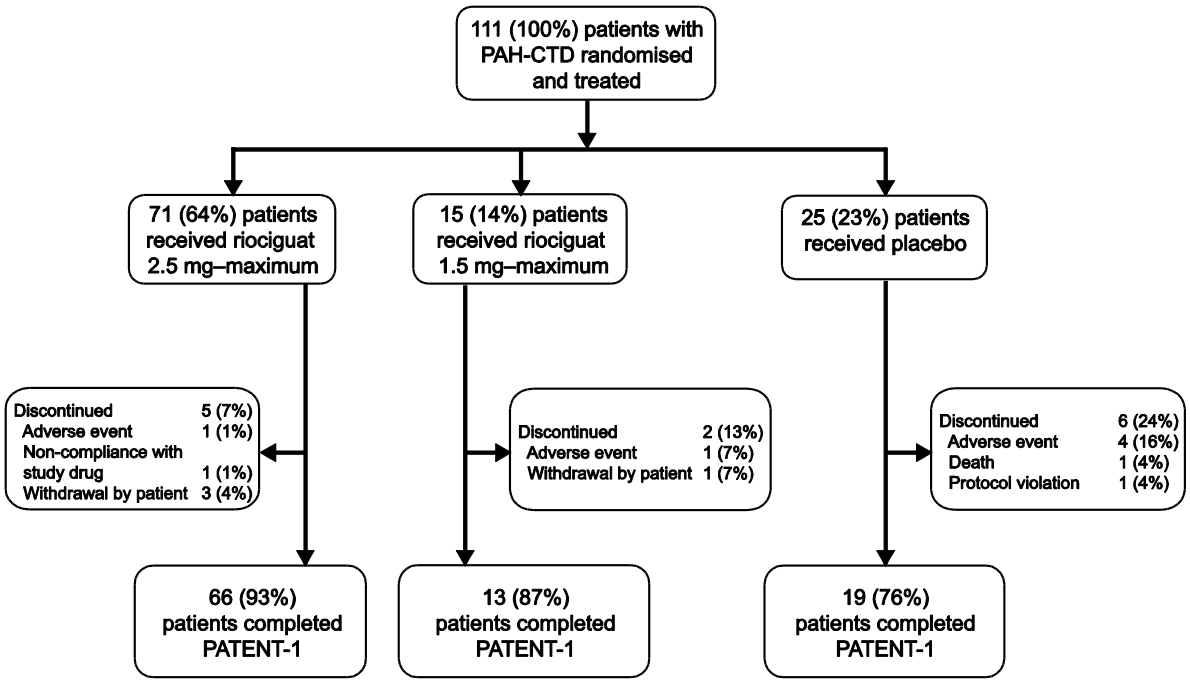
Supplementary Table 6. AEs and SAEs in the overall population and in patients with PAH-CTD in PATENT-2.

	Overall PATENT-2 population (n=396)	Overall PAH-CTD (n=94)	PAH-SSc (n=55)	PAH-other defined CTD (n=34)	Overall PAH-CTD with immunosuppressant use (n=23)
Any AE	388 (98)	93 (99)	55 (100)	33 (97)	23 (100)
AEs occurring in >25% of patients in any group					
Diarrhoea	84 (21)	37 (39)	25 (45)	11 (32)	8 (35)
Peripheral oedema	98 (25)	33 (35)	23 (42)	9 (26)	6 (26)
Nasopharyngitis	118 (30)	31 (33)	15 (27)	14 (41)	7 (30)
Dizziness	101 (26)	32 (34)	17 (31)	13 (38)	7 (30)
Vomiting	67 (17)	23 (24)	19 (35)	4 (12)	8 (35)
Nausea	76 (19)	25 (27)	18 (33)	6 (18)	11 (48)
Pyrexia	31 (8)	11 (12)	2 (4)	9 (26)	4 (17)
Anaemia	50 (13)	14 (15)	7 (13)	7 (21)	6 (26)
Discontinuation due to AE	45 (11)	15 (16)	10 (18)	4 (12)	3 (13)
AEs of special interest					
Hypotension	51 (13)	19 (20)	12 (22)	6 (18)	4 (17)
Syncope	38 (10)	7 (7)	4 (7)	3 (9)	1 (4)
Haemoptysis	27 (7)	3 (3)	2 (4)	1 (3)	0
Any SAE	238 (60)	68 (72)	41 (75)	24 (71)	16 (70)
SAEs experienced by >10% of patients in any group					
Worsening PAH	41 (10)	13 (14)	8 (15)	5 (15)	4 (17)
Right ventricular failure	33 (8)	10 (11)	6 (11)	4 (12)	0
Lupus	4 (1)	4 (4)	0	4 (12)	2 (9)
Lower respiratory tract infection	4 (1)	3 (3)	3 (6)	0	2 (9)

Discontinuation due to SAE	36 (9)	12 (13)	7 (13)	4 (12)	2 (9)

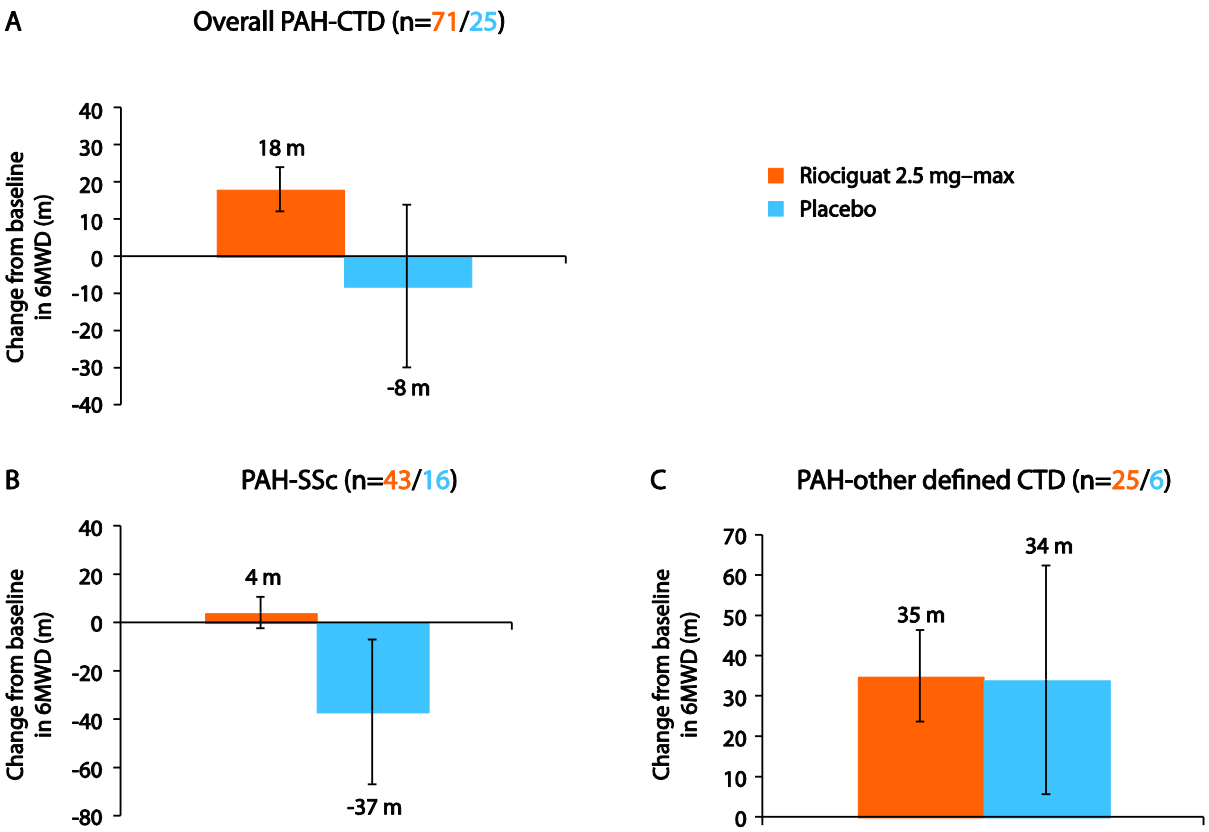
AE, adverse event; CTD, connective tissue disease; PAH, pulmonary arterial hypertension; SAE, serious adverse event; SSc, systemic sclerosis.

Supplementary Figure 1. Patient disposition for patients with PAH-CTD in PATENT-1



CTD, connective tissue disease; PAH, pulmonary arterial hypertension; PAH-CTD, PAH associated with CTD.

Supplementary Figure 2. Change from baseline in 6MWD at Week 12 in PATENT-1 for patients with PAH-CTD



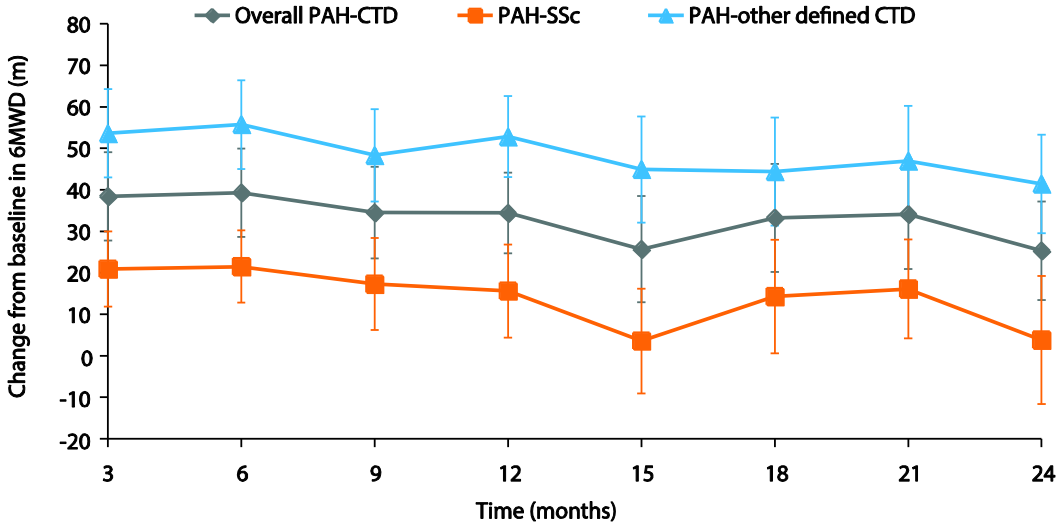
Missing values, where the patient withdrew or died, were imputed at Week 12 according to the last observed value, except in cases of death or clinical worsening without termination visit, when worst value (0 m) was imputed. Graphs show mean±SEM.

6MWD, 6-minute walking distance; CTD, connective tissue disease; PAH, pulmonary arterial hypertension; PAH-CTD, PAH associated with CTD; SSc, systemic sclerosis.

Missing values, where the patient withdrew or died, were imputed at Week 12 according to the last observed value, except in cases of death or clinical worsening without termination visit, when worst value (0 m) was imputed. Graphs show mean±SEM.

6MWD, 6 minute walking distance; CTD, connective tissue disease; PAH, pulmonary arterial hypertension; PAH-CTD, PAH associated with CTD; SSc, systemic sclerosis

Supplementary Figure 3. Change from baseline over time in 6MWD in patients with PAH-CTD in PATENT-2



No. of patients								
Overall PAH-CTD	90	87	80	79	76	69	65	65
PAH-SSc	51	48	44	44	42	37	34	35
PAH-other defined CTD	34	34	32	32	30	28	27	26

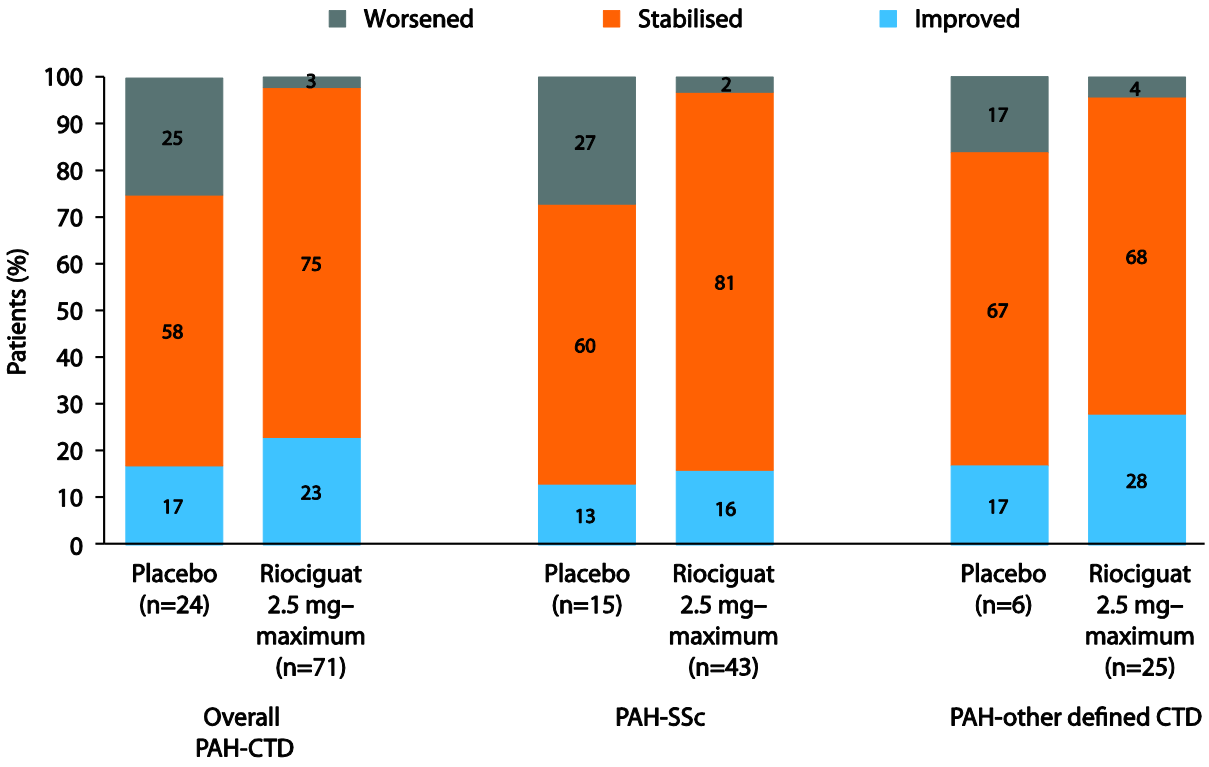
2-year data cut-off March 2014; data are mean±SEM, observed values; baseline is defined as baseline of PATENT-1
Mean±SD treatment duration (months): PAH-CTD, 31±14; PAH-SSc, 29±15; PAH-other defined CTD, 35±12.

6MWD, 6-minute walking distance; CTD, connective tissue disease; PAH, pulmonary arterial hypertension; PAH-CTD, PAH associated with CTD; SSc, systemic sclerosis; SD, standard deviation; SEM, standard error of the mean.

2-year data cut-off March 2014; data are mean±SEM, observed values; baseline is defined as baseline of PATENT-1
Mean±SD treatment duration (months): PAH-CTD, 31±14; PAH-SSc, 29±15; PAH-other defined CTD, 35±12

6MWD, 6 minute walking distance; CTD, connective tissue disease; PAH, pulmonary arterial hypertension; PAH-CTD, PAH associated with CTD; SSc, systemic sclerosis

Supplementary Figure 4. Change from baseline in World Health Organisation functional class at Week 12 of PATENT-1 in patients with PAH-CTD



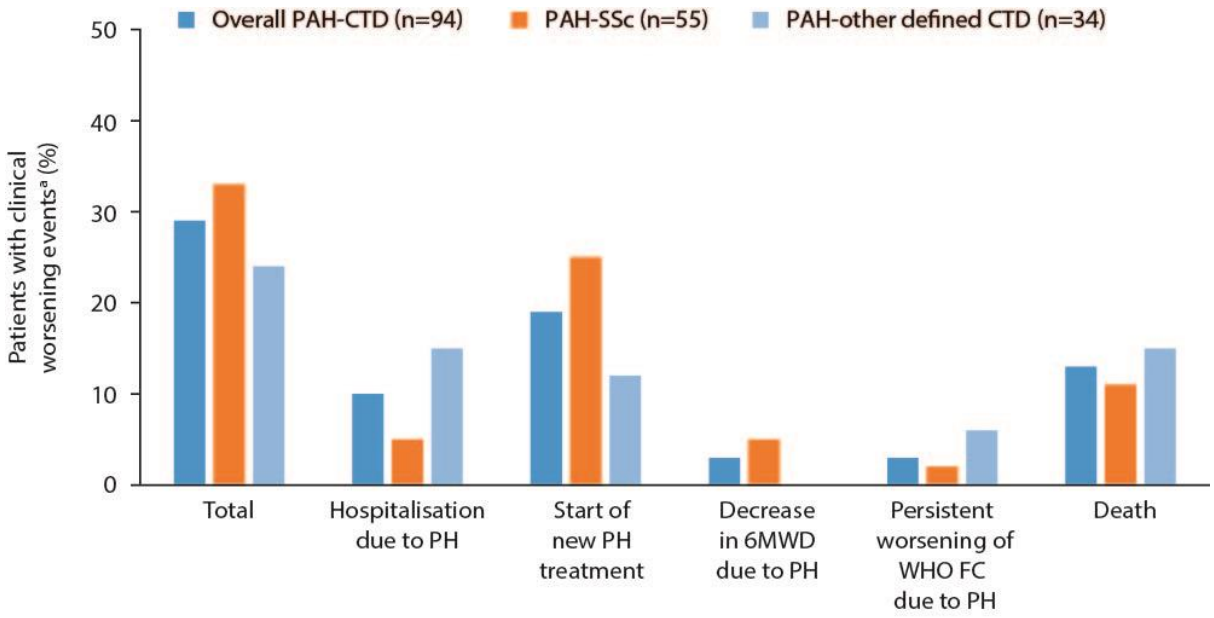
Missing values, where the patient withdrew or died, were imputed at Week 12 according to the last observed value.
In the case of withdrawal due to clinical worsening with no termination visit, the worst possible score (IV) was used; in the case of death, the worst possible value plus one (V) was used.

CTD, connective tissue disease; PAH, pulmonary arterial hypertension; PAH-CTD, PAH associated with CTD; SSc, systemic sclerosis; WHO FC, World Health Organization functional class.

Missing values, where the patient withdrew or died, were imputed at Week 12 according to the last observed value. In the case of withdrawal due to clinical worsening with no termination visit, the worst possible score (IV) was used; in the case of death, the worst possible value plus one (V) was used.

CTD, connective tissue disease; PAH, pulmonary arterial hypertension; PAH-CTD, PAH associated with CTD; SSc, systemic sclerosis

Supplementary Figure 5. Clinical worsening in patients with PAH-CTD in PATENT-2



[a]One patient can experience more than one worsening event
Mean±SD treatment duration (months): PAH-CTD, 31±14; PAH-SSc, 29±15; PAH-other defined CTD, 35±12.

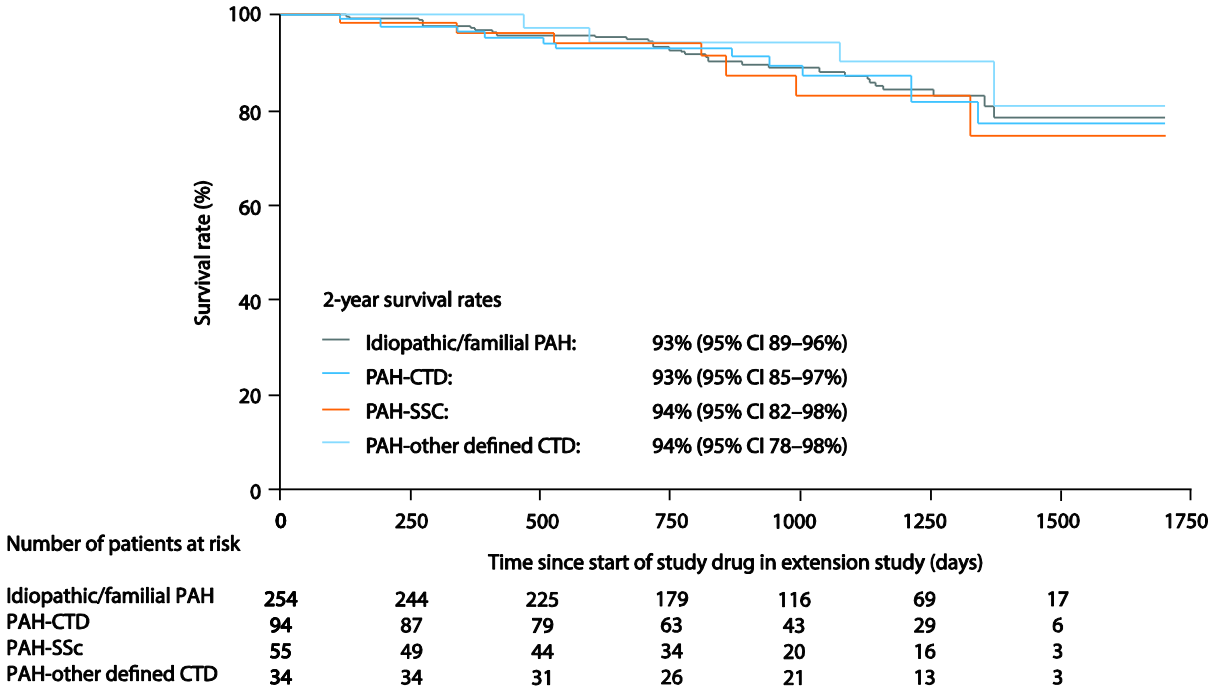
6MWD, 6-minute walking distance; CTD, connective tissue disease; PAH, pulmonary arterial hypertension; PAH-CTD, PAH associated with CTD; SSc, systemic sclerosis; WHO FC, World Health Organization functional class.

[a]One patient can experience more than one worsening event

Mean±SD treatment duration (months): PAH-CTD, 31±14; PAH-SSc, 29±15; PAH-other defined CTD, 35±12

6MWD, 6 minute walking distance; CTD, connective tissue disease; P(A)H, pulmonary (arterial) hypertension; PAH-CTD, PAH associated with CTD; SSc, systemic sclerosis; WHO FC, World Health Organisation functional class

Supplementary Figure 6. Kaplan–Meier survival curves for patients with PAH-CTD in PATENT-2



Number of patients at risk

Idiopathic/familial PAH	254	244	225	179	116	69	17
PAH-CTD	94	87	79	63	43	29	6
PAH-SSc	55	49	44	34	20	16	3
PAH-other defined CTD	34	34	31	26	21	13	3

2-year data cut-off March 2014
Mean±SD treatment duration (months): PAH-CTD, 31±14; PAH-SSc, 29±15; PAH-other defined CTD, 35±12.

CTD, connective tissue disease; PAH, pulmonary arterial hypertension; PAH-CTD, PAH associated with CTD; SSc, systemic sclerosis.

2-year data cut-off March 2014

Mean±SD treatment duration (months): PAH-CTD, 31±14; PAH-SSc, 29±15; PAH-other defined CTD, 35±12

CTD, connective tissue disease; PAH, pulmonary arterial hypertension; PAH-CTD, PAH associated with CTD; SSc, systemic sclerosis