Riociguat in patients with early diffuse cutaneous systemic sclerosis (RISE-SSc): randomised, double-blind, placebo-controlled multicentre trial

Dinesh Khanna,[1] Yannick Allanore,[2] Christopher P. Denton,[3] Masataka Kuwana,[4] Marco Matucci-Cerinic,[5] Janet E. Pope,[6] Tatsuya Atsumi,[7] Radim Bečvář,[8] László Czirják,[9] Eric Hachulla,[10] Tomonoro Ishii,[11] Osamu Ishikawa,[12] Sindhu R. Johnson,[13] Ellen De Langhe,[14] Chiara Stagnaro,[15] Valeria Riccieri,[16] Elena Schiopu,[17] Richard M. Silver,[18] Vanessa Smith,[19] Virginia Steen,[20] Wendy Stevens,[21] Gabriella Szücs,[22] Marie-Elise Truchetet,[23] Melanie Wosnitza,[24] Kaisa Laapas,[25] Janethe de Oliveira Pena, †[26] Zhen Yao,*[27] Frank Kramer,[24] Oliver Distler[28]

Correspondence to:

Prof. Dinesh Khanna, Division of Rheumatology, Department of Internal Medicine, University of Michigan Scleroderma Program, Ann Arbor, MI 48109, USA

khannad@med.umich.edu

Oliver Distler, Department of Rheumatology, University Hospital, Zürich, Zürich 8091, Switzerland.

Oliver.Distler@usz.ch

Dinesh Khanna ORCID iD https://orcid.org/0000-0003-1412-4453

ABSTRACT

Objectives Riociguat is approved for pulmonary arterial hypertension (PAH) and has antiproliferative, anti-inflammatory and antifibrotic effects in animal models of tissue fibrosis. We evaluated the efficacy and safety of riociguat in patients with early diffuse cutaneous systemic sclerosis (dcSSc) at high risk of skin fibrosis progression.

Methods In this randomised, double-blind, placebo-controlled, phase IIb trial, adults with dcSSc of <18 months' duration and a modified Rodnan skin score (mRSS) 10–22 units received riociguat 0.5 mg to 2.5 mg orally three times daily (n=60) or placebo (n=61). The primary endpoint was change in mRSS from baseline to week 52.

Results At week 52, change from baseline in mRSS units was –2.09 ± 5.66 (n=57) with riociguat and –0.77 ± 8.24 (n=52) with placebo (difference of least squares means –2.34 [95% confidence interval, –4.99 to 0.30; p=0.08]). In patients with interstitial lung disease (ILD), forced vital capacity declined by 2.7% with riociguat and 7.6% with placebo. At week 14, average Raynaud's condition score had improved ≥50% in 19/46 patients (41.3%) with riociguat and 13/50 patients (26.0%) with placebo. Safety assessments showed no new signals with riociguat and no treatment-related deaths.

Conclusions Riociguat did not significantly benefit mRSS versus placebo at the predefined $p<0.05$. Secondary and exploratory analyses showed potential efficacy signals that should be tested in further trials. Riociguat was well tolerated.

Keywords: systemic sclerosis; treatment; disease activity

Key messages

What is already known about this subject?

- There is a need for new therapies for patients with diffuse cutaneous systemic sclerosis (dcSSc).
- The soluble guanylate cyclase stimulator riociguat has antiproliferative, anti-inflammatory and antifibrotic effects in vitro and in animal models of tissue fibrosis and has been shown to increase digital blood flow in patients with Raynaud's phenomenon (RP).

What does this study add?

- The RISE-SSc study failed to meet its primary endpoint of change in mRSS after 52 weeks at p=0.08. However, some secondary and exploratory endpoints showed potential efficacy signals that should be investigated in further trials. Riociguat was well tolerated, with no unexpected safety signals.

How might this impact on clinical practice or future developments?

- Although the primary endpoint was not significant, this Phase IIb study provides important information that can inform future study design and gave preliminary findings that could be explored in future trials in patients with dcSSc.

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterised by fibrosis, inflammation and microvascular injury.[1–3] Systemic organ manifestations include pulmonary arterial hypertension (PAH), interstitial lung disease (ILD), Raynaud's phenomenon (RP), and digital ulcers (DU).[3, 4] To date, nintedanib is the only approved therapy for the treatment of SSc-ILD.[5, 6] Thus there is a significant unmet need, particularly in diffuse cutaneous SSc (dcSSc).[3]

The soluble guanylate cyclase (sGC) stimulator riociguat increases intracellular cyclic guanosine monophosphate (cGMP).[7] cGMP activates protein kinases G, which are important in the regulation of vascular tone and remodelling.[8] Riociguat was approved for treatment of PAH following the phase III PATENT-1 study, which included a subgroup with PAH-SSc, in which riociguat prevented the decline in 6-minute walking distance seen with placebo.[9] In a single-dose pilot study, riociguat increased digital blood flow in patients with RP.[10] Riociguat has demonstrated antiproliferative, anti-inflammatory and antifibrotic effects mediated by attenuation of transforming growth factor beta-1 signalling in animal models and in vitro studies.[7, 8, 11–14] sGC stimulators prevented and treated fibrosis in models of SSc.[12, 15]

We hypothesised that riociguat may benefit tissue fibrosis in dcSSc. The **RI**ociguat **S**afety and **E**fficacy in patients with diffuse cutaneous **S**ystemic **Sc**lerosis (RISE-SSc) trial compared riociguat with placebo in patients with early dcSSc.[16–18]

METHODS

Design overview

RISE-SSc (Clinicaltrials.gov identifier: NCT02283762[19]) was a randomised, double-blind, placebo-controlled, parallel group, phase IIb, international, multicentre study, consisting of a screening phase (≤2 weeks), a 52-week, double-blind, main treatment phase, and a long-term extension (online supplementary figure S1; online supplementary file 2). All patients provided written informed

consent. Each site's institutional review board or ethics committee approved the protocol. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice.

Study participants

Investigators enrolled patients ≥18 years old, fulfilling ACR/EULAR classification criteria for SSc,[20] with dcSSc according to LeRoy and Medsger.[21] Based on EUSTAR cohort observations,[16–18] entry criteria specified disease duration ≤18 months (defined as time from first non-RP manifestation) and modified Rodnan skin score (mRSS) 10–22 units to enrich the study with patients at risk of skin fibrosis progression. Other inclusion criteria were per cent predicted forced vital capacity (FVC%) ≥45% and haemoglobin-corrected per cent predicted diffusing capacity of the lung for carbon monoxide (DL_{CO}) ≥40% at screening. Patients receiving concomitant nitrates, nitric oxide donors, phosphodiesterase inhibitors, or recent SSc therapies were excluded (online supplementary file 1, ps 1−3).

Randomisation and intervention

Patients were randomised 1:1 to riociguat or matching placebo, individually adjusted every 2 weeks from 0.5 mg to 2.5 mg orally three times daily over 10 weeks and continued throughout the treatment phase. From week 26, rescue therapy was permitted at investigator discretion (online supplementary file 1, p4). Physical examination, disease status and demographics were obtained at day 0. Disease status was re-evaluated at weeks 12, 26 and 52, with additional assessments of mRSS and pulmonary function at week 39. Raynaud's condition score was assessed by a patient diary completed daily for 7 consecutive days before the first treatment dose and at week 14. Safety assessments included laboratory assessments at screening, on day 0, and at weeks 2, 4, 6, 8, 10, 26, 39, and 52, and evaluation of vital signs, adverse events (AEs), and serious adverse events (SAEs) coded by Medical Directory for Regulatory Activities (MedDRA) preferred terms, DU net burden and prior and concomitant therapy at every visit.

Outcomes and follow-up

The primary endpoint was the change in mRSS from baseline to week 52. To prevent interobserver variability, the same physician, experienced in skin scoring, scored the same patient throughout the study. Skin fibrosis was also analysed by prespecified exploratory analyses of mRSS progression (increase by >5 units and ≥25% from baseline) and regression (decrease by >5 units and ≥25% from baseline). This definition was based on analyses suggesting that a reduction in mRSS of 3.2−5.3 units or 15−25% from baseline is considered a minimally clinically important difference.[22, 23] In addition, descriptive analysis in prespecified patient subgroups was performed (online supplementary file 1, p4). Secondary endpoints were tested hierarchically in the order: American College of Rheumatology Composite Response Index for Systemic Sclerosis (ACR CRISS) at week 52[24] (online supplementary file 1, p5−6), Health Assessment Questionnaire Disability Index (HAQ-DI), patient's global assessment, physician's global assessment, and change in FVC%. An independent, blinded Adjudication Committee reviewed clinical outcomes potentially representing systemic organ manifestations of dcSSc (online supplementary file 1, p6), and all causes of death.

FVC% and DL_{CO}% were assessed overall and (post-hoc) in patients with ILD according to medical history and restrictive lung disease (FVC% 50–75% at baseline).

Effects on RP at week 14 versus day 0 and net DU burden were prespecified exploratory analyses. For details of other prespecified exploratory analyses and post-hoc assessments see online supplementary file 1, p6.

Statistical analysis

Assuming a standard deviation (SD) of 8 mRSS units,[25] 80% power, a 2-sided significance level of 5%, and 1:1 randomisation, 128 patients would be required to detect a placebo-adjusted difference of 4 units for intent-to-treat analysis of mRSS. Endpoints were analysed using mixed model repeated measures, with baseline mRSS as a covariate; treatment arm, region and study visit, the interaction effect between study visit and treatment arm as fixed effects, and patient-specific random effects (online supplementary file 3). The primary endpoint was also analysed by analysis of covariance with

baseline mRSS as a covariate, and treatment arm and region as main effects. Endpoints present or not were estimated using Mantel−Haenszel weights. Analyses were performed on all patients randomised and treated with study medication using SAS 9.2 software (SAS Institute Inc., Cary, NC, USA). Since the primary endpoint was not met, all other p-values are nominal, are only shown for predefined but not post-hoc analyses, cannot be considered statistically significant and are presented for information only.

Patient involvement

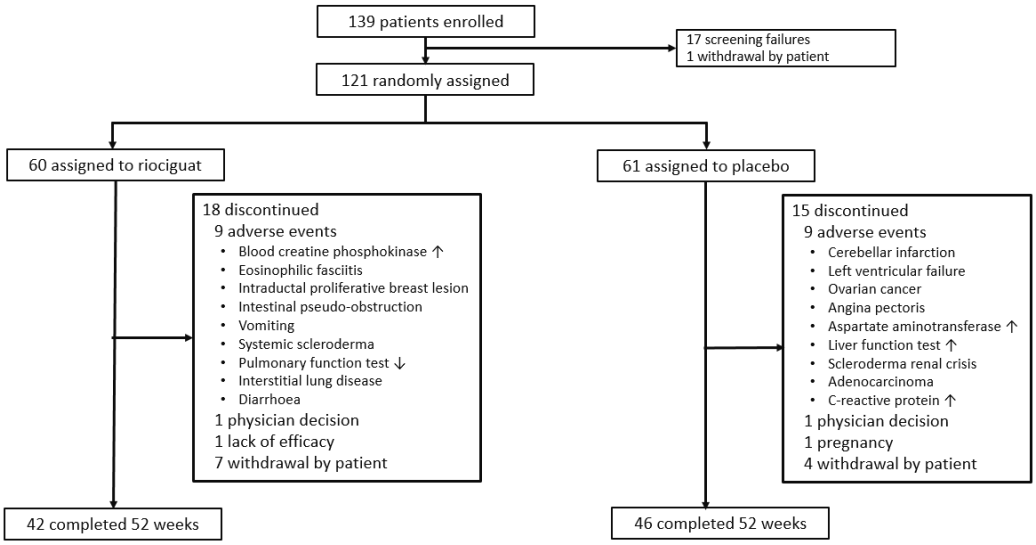
Patients were not directly involved in the design, recruitment or conduct of the study.

RESULTS

Study population

In total, 121 patients were randomised (riociguat, n=60; placebo, n=61). The study was completed according to protocol. Five patients in each group received ≥1 new rescue therapy after week 26. Study discontinuation occurred in 18 riociguat-treated patients (30.0%) and 15 placebo-treated patients (24.6%) (figure 1).

Figure 1 Patient disposition.



At week 52, 34/42 riociguat-treated patients (80.9%) were receiving riociguat 2 or 2.5 mg three times daily. Patients generally had early dcSSc, with mean mRSS 17 and mean disease duration 8.6 months. Baseline characteristics were generally well balanced across groups (table 1).

Table 1 Baseline characteristics of study participants

Characteristic	Overall (n=121)	Riociguat (n=60)	Placebo (n=61)
Mean age (SD), *y*	50.7 (12.2)	51.9 (11.5)	49.5 (12.9)
Female, n *(%)*	92 (76.0)	47 (78.3)	45 (73.8)
White, n *(%)*	89 (73.6)	43 (71.7)	46 (75.4)
Black, n (%)	5 (4.1)	2 (3.3)	3 (4.9)
Asian, n (%)	24 (19.8)	12 (20.0)	12 (19.7)
Native Hawaiian or other Pacific Islander, n (%)	1 (0.8)	1 (1.7)	0
Not reported, n (%)	2 (1.7)	2 (3.3)	0
Mean disease duration (SD), months (from first non-RP manifestation)	9.0 (6.4)	9.5 (7.0)	8.6 (5.8)
Mean mRSS (SD), units	16.8 (3.7)	16.9 (3.4)	16.7 (4.1)
Mean % predicted FVC (SD), %	92.8 (17.8)	90.7 (18.5)	94.8 (17.0)
Mean % predicted DL_{CO} (Hb corr.), (SD), %	76.4 (18.5)	76.0 (19.9)	76.8 (17.2)
Swollen joint count ≥1, n (%)	38 (31.4)	23 (38.3)	15 (24.6)
Mean swollen joint count (SD), n	2.0 (4.7)	3.0 (6.1)	1.1 (2.5)

Tender joint count ≥1, n (%)	51 (42.1)	30 (50.0)	21 (34.4)
Mean tender joint count (SD), n	3.0 (6.2)	3.9 (7.3)	2.1 (4.8)
Digital ulcer count ≥1, n (%)	15 (12.4)	9 (15.0)	6 (9.8)
Mean digital ulcer count (SD), n	0.3 (1.1)	0.3 (0.7)	0.4 (1.4)
Mean digital ulcer count in patients with ulcers (SD), n	2.5 (2.3)	1.7 (1.0)	3.7 (3.2)
Tendon friction rubs ≥1, n (%)	35 (28.9)	15 (25.0)	20 (32.8)
Mean tendon friction rubs (SD), n	3.1 (2.2)	2.4 (1.1)	3.6 (2.7)
ILD by medical history, n (%)	25 (20.7)	12 (20.0)	13 (21.3)
Mean HAQ-DI (SD), units	0.79 (0.68)	0.89 (0.67)	0.69 (0.69)
Anti-RNA polymerase III positive, n (%)	26 (21.5)	10 (16.7)	16 (26.2)
Anti-SCl-70 (anti-topoisomerase I) positive, n (%)	49 (40.5)	26 (43.3)	23 (37.7)
Anti-centromere B positive, n (%)	10 (8.3)	4 (6.7)	6 (9.8)

DL_{CO} (Hb corr.), diffusing capacity for CO corrected for haemoglobin;

FVC, forced vital capacity; HAQ-DI, Health Assessment Questionnaire Disability Index; ILD, interstitial lung disease; mRSS, modified Rodnan skin score; SD, standard deviation.

Skin fibrosis

The primary endpoint was not met at the predefined p<0.05. At week 52, mean mRSS was 14.63 (SD 6.56) with riociguat versus 15.73 (SD 10.48) with placebo: difference of least squares (LS) means –2.34 (standard error 1.33): 95% confidence interval (CI), –4.99 to 0.30; relative difference, –14%: p=0.0815. At week 52, the mean change from baseline in mRSS was –2.09 (SD 5.66) with riociguat and –0.77 (SD 8.24) with placebo (figure 2A). Progression of mRSS (increase by >5 units and ≥25% from baseline) was observed in 11/59 patients (18.6%) with riociguat and 22/60 patients (36.7%) with placebo (Mantel–Haenszel estimate of difference: –17.99% [95% CI, –33.57% to –2.40%; nominal p=0.0237]) (figure 2B). Regression rates (decrease by >5 units and ≥25% from baseline) in the riociguat and placebo groups were 27/59 (45.7%) and 18/60 (30.0%), respectively (Mantel–Haenszel estimate of difference: 15.29% [95% CI, –1.98% to 32.57%; nominal p=0.0827]).

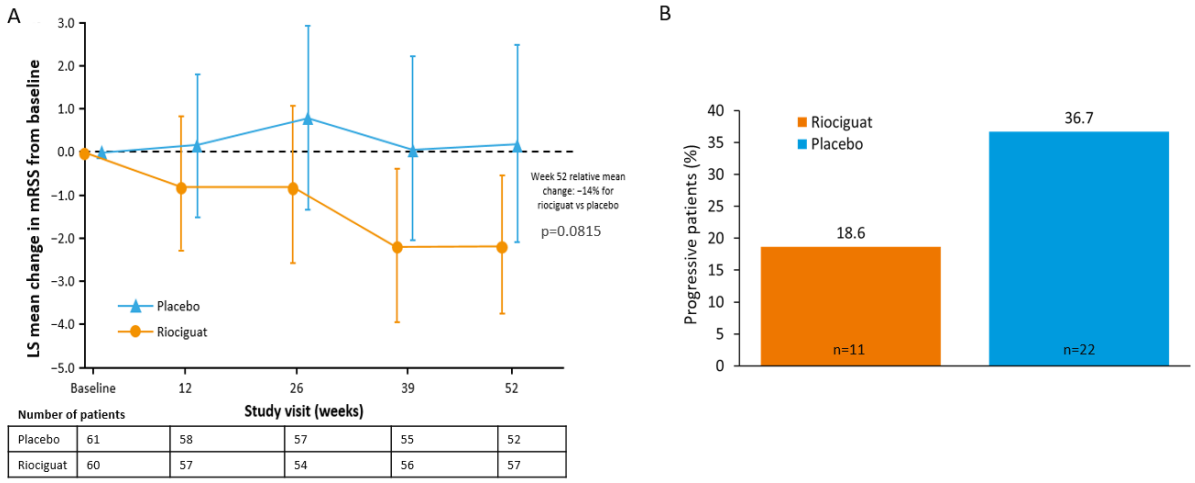


Figure 2 (A) Change from baseline in modified Rodnan skin score (mRSS) during the study. Mixed model with repeated measurement was applied with baseline value, treatment group, region, visit, and treatment by visit interaction as fixed effects, and subject as a random effect. Vertical lines represent 95% CI for change. (B) Proportion of patients with mRSS progression (increase in mRSS by >5 units and ≥25% from baseline: prespecified analysis). Treatment comparison (riociguat −placebo): estimate −17.99%, 95% CI, −33.57 to −2.40. Mantel–Haenszel estimate of difference: nominal p=0.0237. CI, confidence interval; LS, least squares.

On subgroup analyses, the change in mRSS with riociguat versus placebo showed a nominal p-value <0.05 for mRSS 17−22, anti-RNA polymerase III positive/SCl-70 negative, baseline FVC 50−75% and high-sensitivity C-reactive protein (hsCRP) >3.0 mg/L (online supplementary figure S2).

Secondary endpoints

ACR CRISS as a measure of improvement did not show significant differences in this trial designed for prevention of worsening. Eighteen percent of patients in each group had a CRISS improvement probability score ≥0.60 (estimate of difference: 0.20%; [95% CI, –13.68% to 14.09%; nominal p=0.977]). However, on Step 1 of the CRISS analysis, 1 patient (1.7%) in the riociguat group versus 4 (6.6%) in the

placebo group met the definition for SSc-related organ involvement. Other secondary endpoints are shown in table 2.

Table 2 Difference between riociguat group and placebo group in change from baseline to week 52 in secondary endpoints

Endpoint	Riociguat (n=60)	Placebo (n=61)	Estimate of difference (95% CI)	Nominal p-value‡
ACR CRISS				
No improvement, n (%)	1 (1.7)	4 (6.6)		
≥3 missing criteria, n (%)	6 (10.0)	7 (11.5)		
CRISS probability ≥60%, n (%)	11 (18.3)	11 (18.0)	0.20%	
CRISS probability <60%, n (%)	49 (81.7)	50 (82.0)	(–13.68, 14.09)*	0.977
Mean HAQ-DI (SD), units				
Baseline	0.89 (0.67)	0.69 (0.69)	–0.07	
Change at week 52	0.05 (0.38) (n=56)	0.13 (0.42) (n=52)	(–0.23, 0.08)†	0.3529
Mean Patient Global Assessment (SD), units				
Baseline	3.93 (2.50)	3.77 (2.34)	0.79	
Change at week 52	0.69 (2.75) (n=45)	–0.02 (2.23) (n=46)	(–0.12, 1.69)†	0.0887
Mean Physician Global Assessment (SD), units				
Baseline	4.33 (2.11)	4.02 (2.00)	0.83	
Change at week 52	–0.07 (2.16) (n=45)	–0.75 (2.09) (n=47)	(0.11, 1.54)†	0.0241
Mean % predicted FVC (SD), %				
Baseline	90.74 (18.52)	94.82 (17.03)	–0.20	
Change at week 52	–2.38 (7.52) (n=55)	–2.95 (9.73) (n=51)	(–3.40, 3.00)†	0.901

*Mantel–Haenszel estimate.

†Mixed model repeated measures applied with baseline value, treatment group, region, visit, and treatment by visit interaction as fixed effects, and subject as a random effect.

‡Since the primary endpoint was not met, all other p-values cannot be considered statistically significant and are presented for information only.

ACR, American College of Rheumatology; CI, confidence interval; CRISS, Composite Response Index for Systemic Sclerosis; FVC, forced vital capacity; HAQ-DI, Health Assessment Questionnaire Disability Index; SD, standard deviation.

Lung function

Overall, the change in FVC% between baseline and week 52 was −2.38% (SD 7.52) with riociguat and −2.95% (SD 9.73) with placebo (difference of LS means −0.20 [standard error (SE) 1.61]; 95% CI, −3.40 to 3.00; nominal p=0.901) (figure 3A). Two patients in each group developed new ILD. At baseline, 12 riociguat patients (20.0%) and 13 placebo patients (21.3%) had SSc-ILD by medical history, and 11 (18.3%) and 7 (11.5%), respectively, had baseline FVC% 50–75%. Baseline characteristics by lung fibrosis diagnosis are shown in online supplementary table S1. Depending on the diagnosis, the mean change in FVC% from baseline to week 52 was −7.6 to −8.7% with placebo and +0.7 to −2.7% with riociguat (figure 3B).

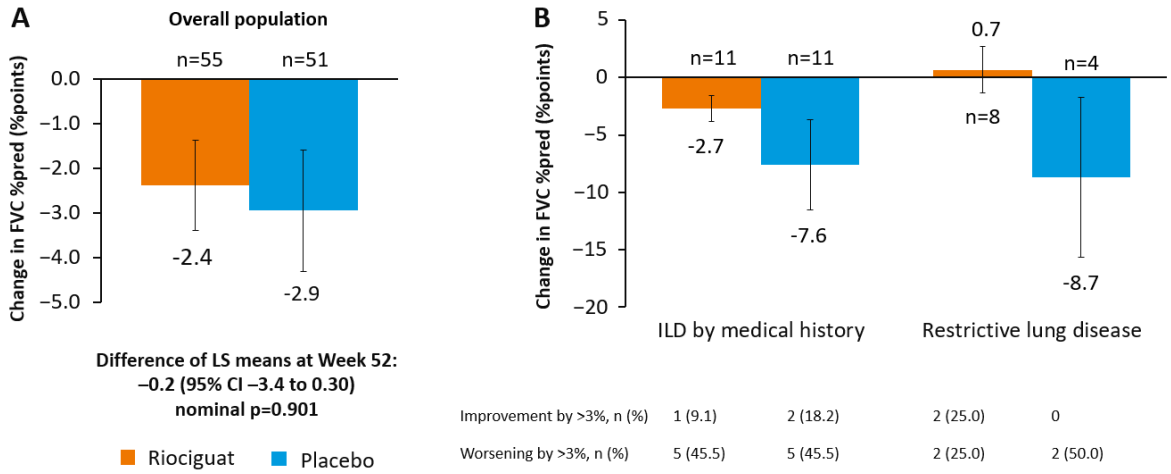


Figure 3 (A) Change in FVC% from baseline to week 52 in overall population. (B) Change in FVC% from baseline to week 52 in patients with lung fibrosis at baseline by diagnostic subgroups (post hoc). Data points are mean (SE). Numbers close to axes are numbers of patients with data at week 52. CI, confidence interval; FVC, forced vital capacity; ILD, interstitial lung disease; LS, least squares; SE, standard error.

DL_{CO}% decreased by −2.31% (SD 10.08) with riociguat and −4.09% (SD 12.19) with placebo (difference of LS means 2.01 [SE 2.14]; 95% CI: −2.24 to 6.25; nominal p=0.3502). In patients with ILD by medical history the changes in DL_{CO}% were –4.55 (SD 8.12) with riociguat (n=11) and –7.63 (SD 13.37) with placebo (n=12). In those with baseline FVC% 50–75%, DL_{CO}% increased by 2.26 (SD 15.16) with riociguat (n=8) and fell by –7.32 (SD 17.24) with placebo (n=5).

Raynaud's phenomenon and digital ulcers

At baseline, 9 patients (15.0%) had DUs in the riociguat group versus 6 (9.8%) in the placebo group. New DUs were reported in 2 patients (3.3%) in the riociguat group and 6 (9.8%) in the placebo group at week 14, and in 5 patients (8.3%) and 12 patients (19.7%), respectively, at week 52. There were 4 and 26 new DUs with riociguat and placebo, respectively, at week 14; and 12 and 72 new DUs, respectively, at week 52 (online supplementary figure 3). Concomitant medication with an indication for DU was used by 7 (11.7%) riociguat patients and 10 (16.4%) placebo patients. Changes from baseline to week 14 in Raynaud's attack duration, frequency and symptoms favoured riociguat but nominally did not differ significantly between riociguat and placebo (online supplementary table S2). The average Raynaud's condition score improved by ≥50% in 19/46 patients (41.3%) with riociguat and in 13/50 patients (26.0%) with placebo. At week 52, reductions in net DU burden were –0.09 (SD 0.50) and –0.08 (SD 1.47) with riociguat and placebo, respectively (difference of LS means –0.11 [SE 0.14] [95% CI: –0.38 to 0.17; nominal p=0.4444]). No case of critical digital ischaemia occurred in either group.

Other endpoints

Findings from prespecified exploratory analyses and post-hoc assessments are provided in online supplementary file 1, p12−19.

Adverse events

Overall, 58 patients in the riociguat group (96.7%) and 55 in the placebo group (90.2%) experienced an AE (online supplementary table S8). Most AEs in the riociguat group were mild to moderate, and most were gastrointestinal events (eg, gastroesophageal reflux disease, diarrhoea, or nausea) or

nervous system disorders (eg, dizziness, headache). Symptomatic hypotension was reported in 7 patients (11.7%) with riociguat and 6 patients (9.8%) with placebo. SAEs were reported in 9 patients (15.0%) in the riociguat group and 15 (24.6%) in the placebo group (table 3). Eleven patients in each group had AEs resulting in discontinuation of study drug (online supplementary table S9). No events of serious haemoptysis were reported. One patient in the riociguat group died from myocardial infarction 117 days after the last administration of riociguat and one patient in the placebo group died from left ventricular failure 157 days after the last administration of placebo. Neither death was considered related to study drug.

Table 3 Serious adverse events

Patients Reporting Event, n (%)		
Event	**Riociguat (n=60)**	**Placebo (n=61)**
Any SAE	9 (15.0)	15 (24.6)
Any study drug-related SAE	0	2 (3.3)
Discontinuation of study drug due to SAE	2 (3.3)	7 (11.5)
Angina pectoris	1 (1.7)	1 (1.6)
Atrial fibrillation	1 (1.7)	0
Abdominal pain	1 (1.7)	0
Intestinal pseudo-obstruction	1 (1.7)	0
Inflammation	1 (1.7)	0
Lung infection	1 (1.7)	0
Pneumonia	1 (1.7)	2 (3.3)
Raynaud's phenomenon	1 (1.7)	1 (1.6)
Musculoskeletal discomfort	1 (1.7)	0
Pain in extremity	1 (1.7)	0
Dyspnoea	1 (1.7)	0
Intraductal proliferative breast lesion	1 (1.7)	0
Pericarditis	0	2 (3.3)
Left ventricular failure	0	1 (1.6)

Ventricular tachycardia	0	1 (1.6)
Gastric haemorrhage	0	1 (1.6)
Gastroesophageal reflux disease	0	1 (1.6)
Nausea	0	1 (1.6)
Vomiting	0	1 (1.6)
Infected skin ulcer	0	1 (1.6)
Anaemia	0	1 (1.6)
Exposure during pregnancy	0	1 (1.6)
Osteolysis	0	1 (1.6)
Scleroderma	0	1 (1.6)
Acute myeloid leukaemia	0	1 (1.6)
Gastric adenocarcinoma	0	1 (1.6)
Ovarian cancer	0	1 (1.6)
Cerebellar infarction	0	1 (1.6)
Syncope	0	1 (1.6)
Scleroderma renal crisis	0	1 (1.6)
Acute pulmonary oedema	0	1 (1.6)
Skin ulcer	0	1 (1.6)
Surgical/medical prophylaxis	0	1 (1.6)

MedDRA preferred terms are shown.

SAE, serious adverse event.

Of those with ILD by medical history, AEs were reported in 10/12 patients (83.3%) with riociguat and 12/13 patients (92.3%) with placebo. AEs reported more frequently with riociguat than with placebo were predominantly dizziness and gastrointestinal events (online supplementary table S10). The incidence of respiratory, thoracic, and mediastinal AEs was similar with riociguat (5 patients; 41.7%) and placebo (5 patients; 38.5%). SAEs were reported in 3/12 (25.0%) and 1/13 patients (8.3%), respectively. Safety in patients with baseline FVC% 50–75% showed no excess AEs with riociguat (online supplementary table S11).

DISCUSSION

RISE-SSc investigated the effects of riociguat on disease progression in patients with early dcSSc. mRSS was selected as the primary endpoint as it correlates with biopsy measures of skin thickness and reflects disease prognosis and visceral involvement.[1, 26] mRSS does, however, have challenging and unpredictable changes over the disease course and attempts to enrich trial populations with patients likely to progress have not been successful. Nevertheless, it is a validated surrogate marker of disease progression[27] and is accepted by authorities as an endpoint for skin fibrosis.[22] RISE-SSc was the first trial in SSc with the EUSTAR inclusion criteria designed to enrich the population with patients likely to show progression of skin fibrosis. Between baseline and week 52, 36.7% of placebo-treated patients showed skin fibrosis progression, which is much higher than in similar trials, [25, 28–30] showing that our enrichment strategy was successful. This is consistent with other evidence that patients with baseline mRSS 15−22 and early disease showed higher progression rates than unselected cohorts.[17, 18, 31]

There are several potential reasons why the primary endpoint was not met in this study. First, RISE-SSc was designed to detect a placebo-adjusted change of mRSS between riociguat and placebo with 80% power. For the low baseline mRSS expected in this study, a 4-unit change would represent a change of 23%. The between-groups difference was 2.3, which was less than expected. This low treatment effect was probably the main reason why the primary endpoint was not met. In addition, the higher than expected numbers of skin fibrosis regressors[18] and stable patients reduced the sensitivity of RISE-SSc to detect a significant change of mRSS. This is consistent with previous trials, in which mRSS improvements were observed in the majority of patients receiving placebo.[32, 33] Other possible explanations include the very large variation in mRSS scores during the study.
As expected, the combined secondary endpoint did not favour riociguat because the ACR CRISS evaluates disease improvement, whereas RISE-SSc was designed to detect prevention of progression. ACR CRISS is not expected to be positive in such a trial design.[24]

Some measures of mRSS, lung function in patients with evidence for pre-existing ILD and the prevention of new DU and RP symptoms suggest potential signals for efficacy. It is important to note that the descriptive analyses of predefined secondary and exploratory endpoints should not be interpreted as efficacy of riociguat, but as a potential signal that can be investigated in further studies.

AEs reported more frequently with riociguat than placebo were mainly gastrointestinal events, dizziness or peripheral oedema. These events are consistent with the effects of riociguat, such as relaxation of smooth muscle cells in the vasculature (often associated with blood pressure decrease) or the gastrointestinal tract and did not increase the incidence of withdrawal due to AEs. SAEs were less common with riociguat than with placebo, no riociguat-treated patient experienced an SAE considered related to study treatment, and fewer discontinued study medication because of an SAE with riociguat than with placebo. Riociguat was, therefore, well tolerated in early dcSSc, particularly when compared with traditional immunosuppressive agents.[34, 35] Tolerability was also good in patients with ILD, which is important given the increased rates of death and SAEs with riociguat in a study in patients with pulmonary hypertension associated with idiopathic interstitial pneumonia.[36]

Discontinuation rates (≈30% with riociguat and ≈25% with placebo) were higher in RISE-SSc than with active treatment in recent trials of abatacept (23%)[37] or tocilizumab (9%)[38] in SSc. RISE-SSc recruited patients with very early disease (compared to these trials, which recruited patients with ≤36 and ≤60 months from onset of SSc, respectively). The early discontinuation may be related to the expectation of worsening of SSc in early disease (based on natural history), where AEs may lead the investigator to withdraw the patient (online supplementary table S9), especially in a placebo-controlled trial. Indeed, another trial with a comparable very early disease population showed a discontinuation rate of 40% in the active treatment (CAT-192) group.[39] Another explanation might be anxiety associated with early disease in the participants; however, these are speculations and should be explored in other trials in patients with very early disease. AEs in the riociguat and placebo groups contributed substantially to the discontinuations in the current study.

In conclusion, RISE-SSc failed to meet its primary endpoint and is therefore a negative trial. However, it provides important findings for the identification of patients at high risk of skin fibrosis progression that could inform future studies in patients with dcSSc. In addition, there are potential efficacy signals in early dcSSc and these may be explored further with additional randomised controlled trials.

AUTHOR AFFILIATIONS

[1]Division of Rheumatology, Department of Internal Medicine, University of Michigan Scleroderma Program, University of Michigan, Ann Arbor, MI, USA

[2]Paris Descartes University, Cochin Hospital, Rheumatology Department, Paris, France

[3]University College London Division of Medicine, London, UK

[4]Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Tokyo, Japan

[5]Department of Experimental and Clinical Medicine, University of Florence, Division of Rheumatology AOUC, Florence, Italy

[6]Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON, Canada

[7]Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Japan

[8]Outpatient Department, Institute of Rheumatology, Clinic of Rheumatology, First Faculty of Medicine, Charles University, Prague, Czech Republic

[9]Department of Immunology and Rheumatology, University of Pécs, Medical School, Pécs, Hungary

[10]Centre de référence des Maladies Auto-Immunes, Systémiques rares du Nord et Nord-Ouest (CeRAINO), Service de Médecine Interne Hôpital Claude Huriez, CHRU, Lille, France

[11]Tohuko University, Japan

[12]Department of Dermatology, Gunma University Postgraduate School of Medicine, Maebashi, Japan

[13]Toronto Scleroderma Program, Mount Sinai and Toronto Western Hospitals, Department of Medicine, University of Toronto, Ontario, Canada

[14]Department of Rheumatology, University Hospitals Leuven, Leuven, Belgium

[15]University of Pisa, Pisa, Italy

[16]University of Rome la Sapienza, Rome, Italy

[17]Division of Rheumatology, Department of Internal Medicine, Michigan Medicine University Hospitals, Michigan, USA

[18]Medical University of South Carolina, Charleston, SC, USA

[19]Ghent University Hospital, Ghent University, Ghent, Belgium

[20]Georgetown University, Washington, DC, USA

[21]Department of Rheumatology, St Vincent's Hospital Melbourne, Australia

[22]Division of Rheumatology, Department of Internal Medicine, University of Debrecen, Hungary

[23]Centre de référence des Maladies Auto-Immunes, Systémiques rares de l'Est et du Sud-Ouest (RESO), Rheumatology Department, Bordeaux University Hospital, France

[24]Bayer AG Research & Development, Wuppertal, Germany

[25]StatFinn Oy, Espoo, Finland

[26]Bayer HealthCare, Whippany, NJ, USA

[27]Bayer HealthCare, Beijing, China

[28]Department of Rheumatology, University Hospital, Zürich, Switzerland

*At the time of publication Z Yao is employed by BeiGene, Beijing, China.

[†]At the time of publication J de Oliveira Pena is employed by Acceleron Pharma, Cambridge, MA, USA.

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Khanna D, *et al*. RISE-SSc: a double-blind, randomised study evaluating the efficacy and safety of riociguat for the treatment of patients with diffuse cutaneous systemic sclerosis. European League Against Rheumatism (EULAR) Congress, Madrid, Spain, 14−17 June 2017. *Ann Rheumat Dis* 2017;76(Suppl. 2): Abstract no. AB0627.

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Distler O, *et al.* Efficacy and safety of riociguat in patients with early diffuse cutaneous systemic sclerosis and interstitial lung disease (SSc-ILD): results from the phase IIb RISE-SSc study. European League Against Rheumatism (EULAR) Congress, Madrid, Spain, 12−15 June 2019. *Ann Rheumat Dis* 2019;78(Suppl. 2):167.1–167.

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Data sharing statement

The corresponding authors can provide, upon request, data that underlie the results reported here, after applying necessary measures to guarantee that no individual is identified or identifiable.

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SUPPLEMENTARY DATA FILE 1

Participating Countries in RISE-SSc

We conducted the main phase between 15 January 2015 and 15 December 2017 in 60 outpatient hospital centres in 15 countries: Australia, New Zealand, Canada, USA, Belgium, the Czech Republic, France, Germany, Hungary, Italy, Switzerland, United Kingdom, The Netherlands, Turkey and Japan.

Exclusion Criteria

Patients who met any of the following criteria were excluded from enrolment in the study.

1. Medical and surgical history

- Limited cutaneous SSc at screening.
- Major surgery (including joint surgery) within 8 weeks prior to screening.
- Patients with a history of malignancy in the last 5 years other than non-melanoma skin cell cancers cured by local resection or carcinoma in situ.
- Known hypersensitivity to the study drug (active substance or excipients).

2. Hepatic-related criteria

- Hepatic insufficiency classified as Child-Pugh C:
    - Patients with isolated alanine aminotransferase (AST) or alanine aminotransferase (ALT) >3 × upper limit of normal (ULN) or bilirubin >2 × ULN could be included under the condition of additional monitoring during the trial.

3. Renal-related criteria

- Estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m^2 (Modification of Diet in Renal Disease [MDRD] formula) or on dialysis at the screening visit:
    - Patients entering the trial with eGFR 15−29 mL/min/1.73 m^2 underwent additional monitoring of renal function.

- Because the MDRD formula is thought to cause significant bias for Japanese patients, the equation for Japanese patients is: 194 × serum creatinine (mg/dL)$^{-1.094}$ × age$^{-0.287}$ × 0.739 (if female).
- Any prior history of renal crisis.

4. Cardiovascular-related criteria

- Sitting systolic blood pressure <95 mmHg at the screening visit.
- Sitting heart rate <50 beats per minute at the screening visit.
- Left ventricular ejection fraction <40% prior to screening.

5. Pulmonary-related criteria

- Any form of pulmonary hypertension as determined by right heart catheterisation.
- Pulmonary disease with percent predicted FVC <45% or per cent predicted diffusing capacity of the lung for carbon monoxide (DLCO) (haemoglobin corrected) <40% of predicted at screening.
- Active state of haemoptysis or pulmonary haemorrhage, including those events managed by bronchial artery embolisation.
- Any history of bronchial artery embolisation or massive haemoptysis within 3 months before screening. (Massive haemoptysis was defined as acute bleeding >240 mL in a 24-hour period or recurrent bleeding >100 mL/day over consecutive days.)

6. Laboratory examinations

- Patients with: haemoglobin <9.0 g/dL, white blood cell count <3000/mm^3 (<3 × 10^9/L), platelet count <100 000/mm^3 (<100 × 10^9/L).

7. Prior and concomitant therapy

- Concomitant use of nitrates or nitric oxide donors (such as amyl nitrate) in any form, including topical; phosphodiesterase (PDE) 5 (PDE5) inhibitors (such as sildenafil, tadalafil, vardenafil); and non-specific PDE5 inhibitors (theophylline, dipyridamole).

- Concomitant therapy with prostacyclin analogues. Oral beraprost for the treatment of digital ulcers/Raynaud's disease, and short-term/intermittent therapy of up to 21 days with intravenous prostacyclin analogues for digital/vascular lesions was allowed.
- Treatment with methotrexate, cyclophosphamide, hydroxychloroquine, cyclosporine A, azathioprine, mycophenolate mofetil, rapamycin, colchicine, D-penicillamine, tacrolimus, mizoribine or intravenous immunoglobulin within 4 weeks before the screening visit.
- Treatment with etanercept within 2 weeks; infliximab, leflunomide, certolizumab, golimumab, adalimumab, abatacept or tocilizumab within 8 weeks; or anakinra within 1 week prior to the screening visit.
- Previous treatment with chlorambucil, bone marrow transplantation or total lymphoid irradiation.
- Treatment with rituximab or other anti-CD20 antibodies within the last 6 months before screening.

8. Other

- Pregnant women or breastfeeding women.
- Women of childbearing potential not willing to use adequate contraception and not willing to agree to 4-weekly pregnancy testing from Visit 1 (first administration of study drug) onwards until 30 (+5) days after last study drug intake.
- Any other condition or therapy that would make the patient unsuitable for this study and will not allow participation for the full planned study period.
- Previous assignment to treatment during this study.
- Participation in another clinical study with an investigational drug or medical device within 30 days prior to randomisation (phases I–III clinical studies).

Study Randomisation, Blinding and Intervention

Patients were randomised 1:1 to riociguat or placebo using the IxRS interactive voice response system (Bayer AG, Berlin, Germany), with permutated blocks sized as a multiple of 2. Data remained

blinded until database lock unless a suspected adverse reaction occurred. Patients randomised to placebo underwent sham adjustment during dose adjustment. All packaging was designed to maintain blinding for investigators and patients, and riociguat and placebo tablets looked, smelled and tasted identical. Study data remained blinded until database lock unless a suspected adverse reaction occurred. An independent Data Monitoring Committee reviewed all data for safety.

Rescue Medication

From week 26, rescue therapy (methotrexate, mycophenolate mofetil, cyclophosphamide, azathioprine or hydroxychloroquine) was permitted at investigator discretion for worsening of skin disease, pulmonary function, inflammatory joint disease or myositis.

Subgroup Analyses of Primary Endpoint

Descriptive analyses of the primary endpoint were performed for the following subgroups:

- region (North America, Europe and Australia/New Zealand, East Asia)
- gender (males/females)age (age <65 years/age ≥65 years)
- mRSS at baseline (10−16 units/17−22 units)
- disease duration at baseline (0−6 months, 7−12 months, 13−18 months)
- antibody at baseline (SCL-70, RNA polymerase III, both, neither)
- ILD (defined with preferred terms: interstitial lung disease and pulmonary fibrosis) at baseline (yes/no)
- FVC%, predicted at baseline (<50, 50−75, >75)
- hsCRP elevated at baseline (≤3.0 mg/L, >3.0 mg/L; and ≤10.0 mg/L, >10.0 mg/L)
- use of corticosteroids at baseline (yes/no)
- tendon friction at baseline (yes/no).

Additional Information on Study Endpoints

The key secondary endpoint was the American College of Rheumatology CRISS at week 52.[24] Application of the CRISS algorithm in a randomised clinical trial was a 2-step process. In Step 1, patients were evaluated to determine whether they had met the criteria for not having improved. A

patient was considered not improved and was assigned a probability score of improving of 0.0, irrespective of improvement on other core items, if he/she developed:

1. New scleroderma renal crisis.

2. Decline in per cent predicted FVC ≥15% (relative), confirmed by another FVC% within a month, HRCT to confirm interstitial lung disease (ILD) (if previous HRCT did not show ILD) and per cent predicted FVC <80% (attributable to SSc).

3. New onset of left ventricular failure (defined as ejection fraction ≤45%) or new onset of PAH requiring treatment (attributable to SSc).

For the remaining patients, the probability of improvement was calculated in Step 2, based on the changes in mRSS, per cent predicted FVC, HAQ-DI, patient's global assessment, and physician's global assessment, in which each measure had a probability score between 0 and 1.

The probability of improving (a score between 0.0 and 1.0, inclusive) was calculated for each patient using the equation:

$$\frac{exp[-5.54-0.81*\Delta_{MRSS}+0.21*\Delta_{FVC\%}-0.40*\Delta_{Pt-glob}-0.44*\Delta_{MD-glob}-3.41*\Delta_{HAQ-DI}]}{1+exp[-5.54-0.81*\Delta_{MRSS}+0.21*\Delta_{FVC\%}-0.40*\Delta_{Pt-glob}-0.44*\Delta_{MD-glob}-3.41*\Delta_{HAQ-DI}]}$$

where Δ_{MRSS} indicates the change in mRSS from baseline to week 52, $\Delta_{FVC\%}$ denotes the change in percent predicted FVC from baseline to week 52, $\Delta_{Pt-glob}$ indicates the change in patient global assessment, $\Delta_{MD-glob}$ denotes the change in physician global assessment, and Δ_{HAQ-DI} is the change in HAQ-DI.

If a patient had one or two missing components, then previous non-missing value of that component was be used. Patients with three or more missing CRISS components were assigned a probability of 0.0.

Clinical Outcomes Potentially Representing Systemic Organ Manifestations Related to dcSSc

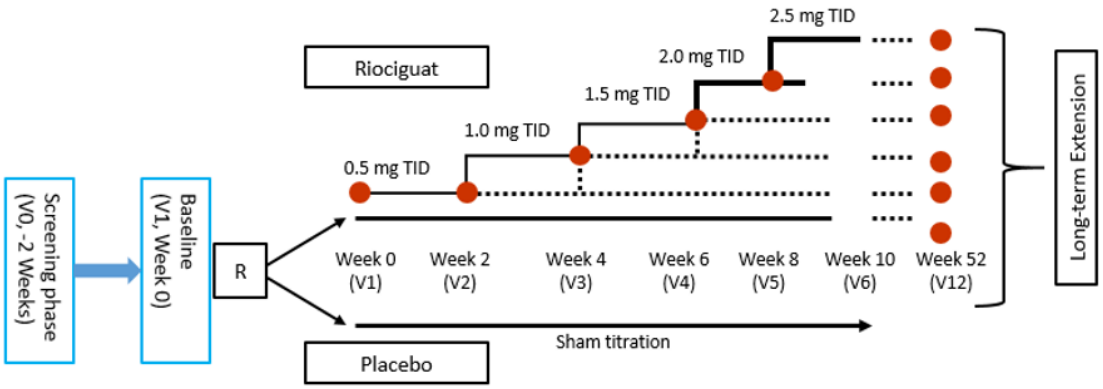
Clinical outcomes potentially representing systemic organ manifestations related to dcSSc were defined in the protocol as follows: new renal crisis; worsening of cardiac disease considered secondary to dcSSc; new-onset pulmonary hypertension requiring treatment; pericardial disease

requiring intervention or exhibiting clinical decompensation; arrhythmias and/or cardiac conduction defects requiring treatment; worsening of gastrointestinal disease requiring hospitalisation or new requirement for parenteral nutrition; critical digital ischaemia requiring hospitalisation; or digital gangrene.

Prespecified Exploratory Analyses and Post-Hoc Assessments

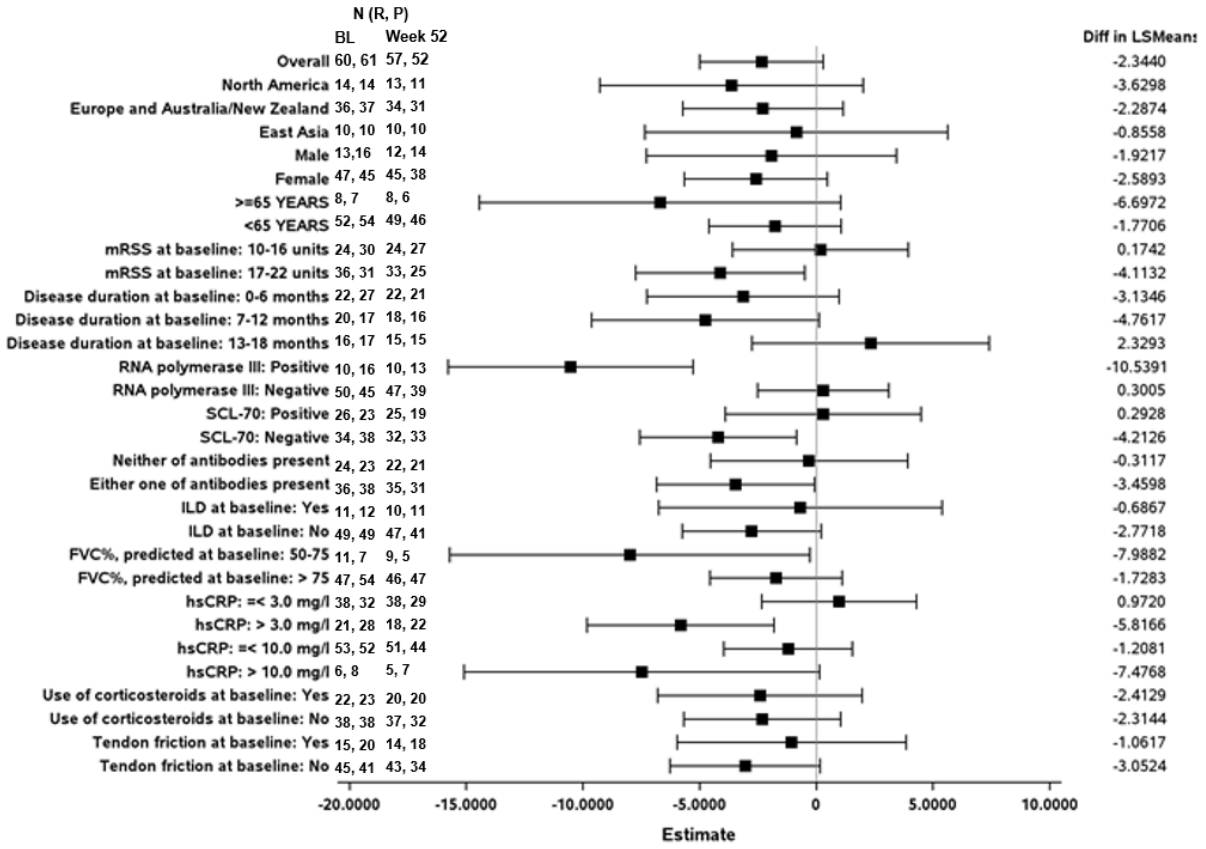
Health-related quality of life using the Short Form 36 (SF-36) Questionnaire version 2.0 and the Scleroderma Health Assessment Questionnaire (S-HAQ) and Patient-Reported Outcomes Measurement Information System (PROMIS)-29 scores (in English-speaking countries) were prespecified exploratory analyses. Clinically significant improvement in HAQ-DI (decrease from baseline ≥0.21 at week 52[40]) and a composite endpoint of disease progression (increase of mRSS ≥4, or absolute decrease of FVC% ≥10%, or new organ involvement as defined in ACR CRISS Step 1) were assessed post hoc.

Supplementary Figure S1. RISE-SSc Trial Design.



R, randomised; TID, three times daily.

Supplementary Figure S2. mRSS Subgroup Analysis at Week 52 (Prespecified Analysis).

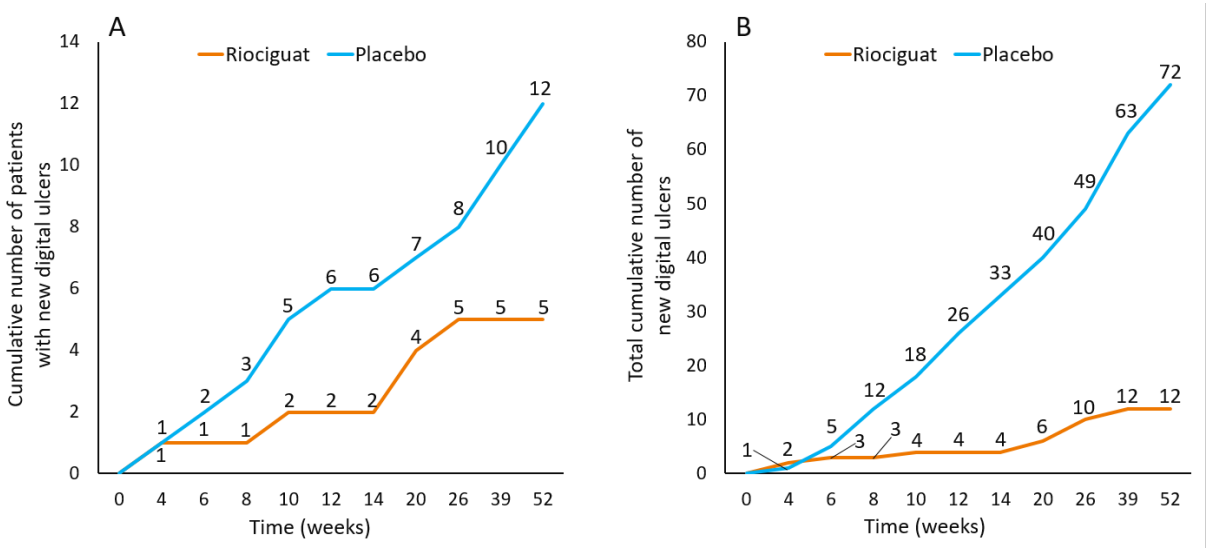


Each square corresponds to the difference in LS means between riociguat and placebo for each subgroup and the line represents the 95% CI. Estimates at week 52 are shown.

Note. hsCRP levels of 3 and 10 mg/L are cut-off levels for assessment of cardiovascular risk or diagnosis of acute infections respectively.

BL, baseline; CI, confidence interval; FVC, forced vital capacity; hsCRP, high-sensitivity C-reactive protein; ILD, interstitial lung disease; LS, least squares; mRSS, modified Rodnan skin score; P, placebo; R, riociguat; RNA, ribonucleic acid; SCL-70, anti-topoisomerase I antibodies.

Supplementary Figure S3. Development of New Digital Ulcers.



A. Cumulative numbers of patients with new digital ulcers. **B.** Cumulative numbers of new digital ulcers.

Digital ulcers are defined as full-thickness skin lesions with loss of epithelium, including lesions covered by eschar. Ulcers should be >3 mm in maximal diameter.

New digital ulcers are defined as ulcers not existing at baseline.

Please note that patients receiving concomitant nitrates, nitric oxide donors, phosphodiesterase inhibitors and long-term prostacyclin analogues therapy were not included in the study, which might have influenced the study population.

Nominal p-values were not calculated for post-hoc analyses.

Supplementary Table S1. Baseline Characteristics of Study Participants with ILD

	ILD by medical history		**FVC% 50–75% at baseline**	
Characteristic	**Riociguat (n=12)**	**Placebo (n=13)**	**Riociguat (n=11)**	**Placebo (n=7)**
Mean age (SD), *y*	58 (8.7)	50 (15.2)	47 (11.5)	49 (16.7)
Female, n (%)	9 (75.0)	10 (76.9)	9 (81.8)	6 (85.7)
White, n (%)	7 (58.3)	8 (61.5)	9 (81.8)	7 (100)
Median (range) disease duration, *months*	6.7 (0.6–44.4)	11.2 (0.9–17.6)	13.8 (6.8–18.0)	12.6 (5.2–16.8)
Mean mRSS (SD), *units*	15.1 (3.9)	16.6 (4.5)	19.3 (2.5)	17.3 (4.7)
Mean % predicted FVC (SD), *%*	82.8 (23.1)	91.0 (21.9)	69.2 (7.9)	70.1 (6.6)
Mean % predicted DL_{CO} (Hb corr.), (SD), *%*	75.7 (22.6)	69.6 (16.2)	67.1 (15.5)	68.7 (15.1)

DL_{CO} (Hb corr.), diffusing capacity for carbon monoxide corrected for haemoglobin; FVC, forced vital capacity; HAQ-DI, Health Assessment Questionnaire Disability Index; ILD, interstitial lung disease; mRSS, modified Rodnan skin score; SD, standard deviation.

Supplementary Table S2. Change in Raynaud´s Attacks from Baseline to Week 14

	Riociguat			**Placebo**			**Nominal p-value†**
	Baseline, mean (SD) (range)	**Absolute change**	**Relative change (%)***	**Baseline, mean (SD) (range)**	**Absolute change**	**Relative change (%)***	
Duration of attacks per day, *min*	38.7 (54.8) (0.0–228.6) (n=58)	–12.9 (n=52)	–33	73.0 (139.8) (0.0–728.6) (n=60)	–14.4 (n=52)	–20	N/A
Attacks per day, n	2.5 (2.7) (0.0–11.6) (n=58)	–1.2 (n=52)	–49	2.0 (2.2) (0.0–12.3) (n=60)	–0.6 (n=52)	–28	N/A
Raynaud's condition score, *units* (range 0–10)	3.1 (2.5) (0.0–8.4) (n=56)	–0.9 (n=45)	–30	2.7 (2.6) (0.0–9.6) (n=60)	–0.4 (n=49)	–13	0.4132
Patient assessment, *units* (range 0–100)	29.1 (26.3) (0.0–94.0) (n=58)	–10.1 (n=49)	–35	26.9 (26.7) (0.0–100.0) (n=60)	–0.8 (n=52)	–3	0.0622
Physician assessment, *units* (range 0–100)	31.5 (24.2) (0.0–83.0) (n=58)	–12.8 (n=50)	–40	36.9 (28.3) (0.0–94.0) (n=61)	–9.6 (n=54)	–26	0.2780
Pain (attack symptom, *units*; range 0–100)	24.6 (25.6) (0.0–82.6) (n=51)	–6.9 (n=40)	–28	21.5 (26.4) (0.0–90.0) (n=57)	–1.8 (n=44)	–9	N/A
Numbness (attack symptom, *units*; range 0–100)	26.0 (25.6) (0.0–89.3) (n=51)	–5.7 (n=39)	–22	22.0 (24.2) (0.0–91.4) (n=57)	–0.2 (n=44)	–1	N/A

Tingling (attack symptom, *units*; range 0–100)	20.9 (23.1) (0.0–81.6) (n=51)	–3.0 (n=39)	–14	16.9 (22.5) (0.0–80.0) (n=57)	+1.4 (n=43)	+8	N/A

*Percentage calculated as mean change from baseline to week 14/mean baseline value × 100.

†Since the primary endpoint was not met, all other p-values cannot be considered statistically significant and are presented for information only.

N/A, not applicable (post hoc analyses); SD, standard deviation.

Prespecified Exploratory Analyses and Post-Hoc Assessments

At week 14, S-HAQ patient-reported interference with daily activities by RP declined by −0.31 (SD 0.67) with riociguat and by −0.11 (SD 0.76) with placebo (difference of LS means –0.12 [SE 0.11]; 95% CI, –0.33 to 0.10; nominal p=0.295).

Adjudicated clinical outcome events related to SSc were reported in 4 patients (6.7%) in the riociguat group and 6 (9.9%) in the placebo group (online supplementary table S3). Changes in PROMIS-29 scores (online supplementary table S4), SF-36 scores (online supplementary table S5) or S-HAQ scores (online supplementary table S6) did not differ substantially between treatment groups. Improvement in HAQ-DI was reported in 11/56 (19.6%) riociguat patients and 7/52 (13.5%) of placebo patients. Time to the composite endpoint of progression was longer with riociguat than with placebo.

Supplementary Table S3. Prespecified Analysis of Adjudicated Clinical Outcome Events

Patients Reporting Event, n (%)		
Event	**Riociguat (n=60)**	**Placebo (n=61)**
Any	4 (6.7)	6 (9.8)
New renal crisis	0	1 (1.6)
Scleroderma renal crisis	0	1 (1.6)
Worsening of cardiac disease defined as new or worsened clinically symptomatic and significant heart disease considered secondary to dcSSc	0	1 (1.6)
Left ventricular failure	0	1 (1.6)
Pericardial disease requiring intervention or exhibiting clinical decompensation	0	1 (1.6)
Category not recorded	0	1 (1.6)
Pericarditis	0	1 (1.6)
Arrhythmias or conduction defects requiring treatment	0	2 (3.3)
Sinus tachycardia	0	1 (1.6)
Ventricular tachycardia	0	1 (1.6)
Worsening gastrointestinal disease requiring hospitalisation	2 (3.3)	0
Abdominal pain	1 (1.7)	0
Intestinal pseudo-obstruction	1 (1.7)	0
New requirement for total parenteral nutrition	1 (1.7)	0
Abdominal pain	1 (1.7)	0
Non-SSc-related events	1 (1.7)	2 (3.3)
Atrial fibrillation	1 (1.7)	0
Pericarditis	0	1 (1.6)
Vomiting	0	1 (1.6)

Unknown	2 (3.3)	1 (1.6)
Atrial fibrillation	1 (1.7)	0
Atrioventricular block	1 (1.7)	0
Gastroesophageal reflux disease	0	1 (1.6)

dcSSc, diffuse cutaneous systemic sclerosis; SSc, systemic sclerosis.

Supplementary Table S4. Change in PROMIS-29 Scores from Baseline to Week 52

Score	**Riociguat**		**Placebo**	
	Mean (SD) score at baseline, *units* (n=22)	**Mean (SD) change at week 52, *units* (n=20)**	**Mean (SD) score at baseline, *units* (n=22)**	**Mean (SD) change at week 52, *units* (n=18)**
Physical function	40.75 (6.49)	–0.81 (4.84)	43.82 (7.77)	–3.73 (7.24)
Anxiety	50.64 (8.85)[†]	–2.21 (9.18)[‡]	50.21 (9.89)	0.51 (7.43)
Depression	48.94 (7.57)[†]	–1.92 (6.80)[‡]	46.37 (8.21)	4.32 (6.94)
Fatigue	56.66 (10.68)[†]	–2.95 (7.39)[‡]	52.61 (11.59)	2.40 (10.27)
Sleep disturbance	51.58 (4.86)	0.83 (3.25)	51.30 (4.73)	1.57 (5.19)
Satisfaction with social role	41.80 (9.06)	3.62 (9.85)	44.49 (11.85)	–1.00 (7.92)
Pain interference	58.02 (8.90)	1.41 (8.30)	55.88 (9.44)	–0.02 (7.18)*

*Estimated treatment difference for LS means (riociguat – placebo at week 52): nominal p=0.4055.

[†]n=21.

[‡]n=19.

LS, least squares; PROMIS-29, Patient-Reported Outcomes Measurement Information System; SD, standard deviation.

Supplementary Table S5. Change in SF-36 Scores from Baseline to Week 52

Score	**Riociguat**		**Placebo**		**Nominal p-value*†**
	Mean (SD) score at baseline, *units* (n=60)	**Mean (SD) change at week 52, *units* (n=56)**	**Mean (SD) score at baseline, *units* (n=61)**	**Mean (SD) change at week 52, *units* (n=52)**	
Bodily pain	53.5 (27.53)	–1.21 (22.23)	57.64 (24.89)	4.17 (22.62)	0.1432
General health	48.03 (20.54)	–4.23 (17.24)	52.92 (21.42)	–5.54 (18.63)	0.8918
Mental health	66.67 (20.08)	0.27 (21.03)	69.43 (18.93)	–0.77 (17.86)	0.9724
Physical functioning	59.92 (26.13)	–2.32 (16.35)	66.39 (25.79)	0.99 (18.11)	0.2245
Role emotional	75.83 (27.73)	–5.36 (31.96)	72.95 (26.16)	–1.92 (28.47)	0.7347
Role physical	59.90 (30.54)	–6.36 (24.06)	62.91 (30.27)	–4.93 (25.28)	0.6886
Social functioning	71.46 (26.95)	–2.23 (24.78)	71.11 (26.17)	–0.48 (27.34)	0.7178
Vitality	47.71 (21.15)	0.67 (14.14)	50.79 (22.13)	0.12 (18.38)	0.8321
Mental component score	47.93 (10.73)	–0.50 (11.57)	47.51 (10.29)	–0.57 (10.35)	0.8613
Physical component score	41.38 (10.32)	–1.42 (6.16)	43.88 (10.33)	–0.34 (6.93)	0.2209
Mental health enhanced score	9.82 (7.06)	0.03 (7.91)	8.82 (6.46)	0.23 (6.31)	0.917
Health utility index	0.65 (0.13)	–0.01 (0.10)	0.66 (0.12)[‡]	0.00 (0.10)[§]	0.6979

*Estimated treatment difference for LS means (riociguat – placebo at week 52).

[‡]n=60.

[§]n=51.

LS, least squares; SD, standard deviation; SF-36, Short Form 36.

[†]Since the primary endpoint was not met, all other p-values cannot be considered statistically significant and are presented for information only.

Supplementary Table S6. Change in S-HAQ Scores from Baseline to Week 52

Score	**Riociguat**		**Placebo**		**Nominal p-value*†**
	Mean (SD) score at baseline, *units* (n=60)	**Mean (SD) change at week 52, *units* (n=56)**	**Mean (SD) score at baseline, *units* (n=61)**	**Mean (SD) change at week 52, *units* (n=52)**	
Pain in past week	1.02 (0.88)	–0.01 (0.78)	0.85 (0.82)	–0.04 (0.66)	0.5952
Intestinal problems in past week	0.49 (0.80)[‡]	0.12 (0.60)[§]	0.37 (0.67)	0.12 (0.67)	0.6803
Breathing problems in past week	0.48 (0.75)	0.05 (0.37)	0.27 (0.51)	0.19 (0.56)	0.1267
Raynaud's in past week	0.72 (0.86)[‡]	0.00 (0.76)[§]	0.70 (0.83)	–0.09 (0.67)	0.6623
Finger ulcers in past week	0.32 (0.70)	0.08 (0.72)	0.30 (0.68)	0.11 (0.74)	0.5205
Overall disease rating	1.01 (0.86)	0.10 (0.78)	1.05 (0.88)	–0.10 (0.83)	0.491

Data are expressed as mean (SD).

*Estimated treatment difference for LS means (riociguat – placebo at week 52).

[‡]n=59.

[§]n=55.

LS, least squares; SD, standard deviation; S-HAQ, Scleroderma Health Assessment Questionnaire.

[†]Since the primary endpoint was not met, all other p-values cannot be considered statistically significant and are presented for information only.

Post-hoc assessment: effects of differences between regions on primary endpoint

An analysis for mRSS with region by treatment interaction term was performed. Three approximately equal-size regions were defined (Europe/Australia/New Zealand, North America, East Asia/Japan). Numerically, Europe/Australia/New Zealand had lower changes in both treatment groups, but no statistically significant differences were found (supplementary table S7). We concluded that the observed differences between regions do not explain the non-significant primary endpoint.

Supplementary Table S7. Mixed Model Repeated Measures (Method #1) for Change from Vaseline to Week 52 in mRSS, Including Treatment by Region Interaction (Full Analysis Set), Least Square Means

Treatment	Interaction term	LS mean of change	Standard error of change	95% CI for change
Riociguat	North America	−2.45	1.41	(−5.28, 0.38)
	Europe /Australia/New Zealand	−0.65	0.89	(−2.44, 1.14)
	East Asia/Japan	−2.21	1.70	(−5.62, 1.20)
Placebo	North America	1.13	1.74	(−2.35, 4.62)
	Europe/Australia/New Zealand	0.04	1.15	(−2.26, 2.33)
	East Asia/Japan	1.02	2.05	(−3.07, 5.10)

For the statistical evaluation, a MMRM model was applied with baseline value, treatment group, region, visit, treatment by visit and treatment by region as fixed effects, and subject as a random effect. Method #1: all observations are used.

CI, confidence intervals; LS, least squares; MMRM, mixed model repeated measures; mRSS, modified Rodnan skin score.

Post-hoc assessment: effects of discontinuation on primary endpoint

To investigate whether the high discontinuation rate may have contributed to the failure to reach statistical significance, we performed, as a sensitivity analysis, tipping point analysis and pattern-mixture modelling to evaluate whether missing values had a large impact on the results. Those analyses were consistent with the primary one. The numbers of drop-outs were similar in both groups. It therefore seems unlikely that the high discontinuation rate contributed to the lack of a significant effect on mRSS.

Supplementary Table S8. Summary of Adverse Events

Patients Reporting Event, n *(%)*		
Event	**Riociguat (n=60)**	**Placebo (n=61)**
Any AE	58 (96.7)	55 (90.2)
Any study drug-related AE	40 (66.7)	29 (47.5)
Any AE related to procedures required by the protocol	4 (6.7)	2 (3.3)
Maximum intensity for any AE		
Mild	17 (28.3)	21 (34.4)
Moderate	35 (58.3)	24 (39.3)
Severe	6 (10.0)	10 (16.4)
Maximum intensity for study drug-related AE		
Mild	25 (41.7)	18 (29.5)
Moderate	15 (25.0)	8 (13.1)
Severe	0	3 (4.9)
Discontinuation of study drug due to AE	11 (18.3)	11 (18.0)
Most common AEs		
Gastroesophageal reflux disease	15 (25.0)	7 (11.5)
Dizziness	13 (21.7)	7 (11.5)
Arthralgia	12 (20.0)	8 (13.1)
Headache	11 (18.3)	12 (19.7)
Diarrhoea	10 (16.7)	8 (13.1)
Cough	9 (15.0)	5 (8.2)
Vomiting	8 (13.3)	6 (9.8)
Dyspnoea	8 (13.3)	5 (8.2)
Palpitations	8 (13.3)	3 (4.9)
Nausea	7 (11.7)	7 (11.5)
Fatigue	7 (11.7)	6 (9.8)
Hypotension	7 (11.7)	4 (6.6)

Dyspepsia	7 (11.7)	2 (3.3)
Peripheral oedema	6 (10.0)	2 (3.3)
Dysphagia	6 (10.0)	1 (1.6)
Skin ulcer	4 (6.7)	8 (13.1)
Upper respiratory tract infection	4 (6.7)	8 (13.1)
Any AE of special interest	7 (11.7)	6 (9.8)
Serious haemoptysis	0	0
Symptomatic hypotension*	7 (11.7)	6 (9.8)

Table shows AEs reported in $\geqslant$10% of patients in either group, and all AEs of special interest.

*This included any patients in whom symptoms, eg, headache or dizziness, were reported as hypotension in the case report form.

AE, adverse event.

MedDRA preferred terms are shown.

Supplementary Table S9. AEs Leading to Discontinuation of Study Drug

Patients Reporting Event, n *(%)*		
Event	**Riociguat (n=60)**	**Placebo (n=61)**
Any AE leading to discontinuation	11 (18.3)	11 (18.0)
Angina pectoris	0	1 (1.6)
Left ventricular failure	0	1 (1.6)
Upper abdominal pain	1 (1.7)	0
Diarrhoea	1 (1.7)	0
Dysphagia	1 (1.7)	0
Haematochezia	1 (1.7)	0
Intestinal pseudo-obstruction	1 (1.7)	0
Vomiting	1 (1.7)	0
Exposure during pregnancy	0	1 (1.6)
Aspartate aminotransferase increased	0	1 (1.6)
Blood creatinine phosphokinase increased	1 (1.7)	0
C-reactive protein increased	0	1 (1.6)
Liver function test increased	0	1 (1.6)
Pulmonary function test decreased	1 (1.7)	0
Eosinophilic fasciitis	1 (1.7)	0
Muscular weakness	1 (1.7)	0
Musculoskeletal pain	0	1 (1.6)
Myositis	0	1 (1.6)
Systemic scleroderma	1 (1.7)	0
Acute myeloid leukaemia	0	1 (1.6)
Intraductal proliferative breast lesion	1 (1.7)	0
Ovarian cancer	0	1 (1.6)
Cerebellar infarction	0	1 (1.6)
Scleroderma renal crisis	0	1 (1.6)

Interstitial lung disease	1 (1.7)	0

AE, adverse event.

MedDRA preferred terms are shown.

Supplementary Table S10. Summary of Adverse Events According to Presence or Absence of ILD by Medical History

Patients Reporting Event, n *(%)*				
	Riociguat Group		**Placebo Group**	
Event	With ILD (n=12)	Without ILD (n=48)	With ILD (n=13)	Without ILD (n=48)
Any adverse event	10 (83.3)	48 (100.0)	12 (93.2)	43 (89.6)
Dizziness	4 (33.3)	9 (18.8)	3 (23.1)	4 (8.3)
Gastro-oesophageal reflux disease	3 (25.0)	12 (25.0)	1 (7.7)	5 (10.4)
Diarrhoea	2 (16.7)	8 (16.7)	1 (7.7)	7 (14.6)
Palpitations	2 (16.7)	6 (12.5)	2 (15.4)	1 (2.1)
Dyspepsia	2 (16.7)	5 (10.4)	0	2 (4.2)
Pain	2 (16.7)	1 (2.1)	0	0
Arthralgia	1 (8.3)	11 (22.9)	2 (15.4)	5 (10.4)
Headache	1 (8.3)	10 (20.8)	3 (23.1)	8 (16.7)
Dyspnoea	1 (8.3)	7 (14.6)	1 (7.7)	4 (8.3)
Cough	1 (8.3)	7 (14.6)	0	5 (10.4)
Fatigue	1 (8.3)	6 (12.5)	2 (15.4)	4 (8.3)
Vomiting	1 (8.3)	6 (12.5)	2 (15.4)	4 (8.3)
Dysphagia	1 (8.3)	5 (10.4)	0	1 (2.1)
Nasopharyngitis	1 (8.3)	4 (8.3)	0	5 (10.4)
Hypotension	0	7 (14.6)	1 (7.7)	3 (6.3)
Nausea	0	6 (12.5)	3 (23.1)	4 (8.3)
Peripheral oedema	0	6 (12.5)	1 (7.7)	1 (2.1)
Peripheral swelling	0	5 (10.4)	1 (7.7)	3 (6.3)
Upper respiratory tract infection	0	4 (8.3)	2 (15.4)	6 (12.5)
Pruritus	0	4 (8.3)	2 (15.4)	3 (6.3)
Urinary tract infection	0	4 (8.3)	2 (15.4)	0

Skin ulcer	0	4 (8.3)	1 (7.7)	7 (14.6)
Abdominal pain	0	3 (6.3)	0	5 (10.4)
Pyrexia	0	2 (4.2)	2 (15.4)	2 (4.2)
Hypertension	0	0	3 (23.1)	1 (2.1)
Sjögren's syndrome	0	0	2 (15.4)	1 (2.1)

ILD was identified by medical history at baseline.

Table shows adverse events reported in ⩾10% of patients in any group.

One patient (8.3%) with ILD receiving riociguat experienced an SAE (pneumonia). Three patients (23.1%) with ILD receiving placebo experienced an SAE. The SAEs reported were angina pectoris, pericarditis, ventricular tachycardia, gastric haemorrhage, osteolysis, gastric adenocarcinoma and syncope, each in 1 patient (7.7%) (some patients experienced >1 SAE).

Supplementary Table S11 Summary of Adverse Events According to Presence or Absence of ILD Defined by FVC% 50−75% at Baseline

Patients Reporting Event, n *(%)*				
	Riociguat Group		**Placebo Group**	
Event	With ILD (n=11)	Without ILD (n=49)	With ILD (n=7)	Without ILD (n=54)
Any adverse event	11 (100)	47 (95.9)	5 (71.4)	50 (92.6)
Dizziness	3 (27.3)	10 (20.4)	1 (14.3)	6 (11.1)
Arthralgia	3 (27.3)	9 (18.4)	2 (28.6)	6 (11.1)
Gastro-oesophageal reflux disease	2 (18.2)	13 (26.5)	2 (28.6)	5 (9.3)
Headache	2 (18.2)	9 (18.4)	2 (28.6)	10 (18.5)
Vomiting	2 (18.2)	6 (12.2)	1 (14.3)	5 (9.3)
Dysphagia	2 (18.2)	4 (8.2)	0	1 (1.9)
Interstitial lung disease	2 (18.2)	2 (4.1)	0	2 (3.7)
Abdominal pain	2 (18.2)	1 (2.0)	0	5 (9.3)
Conjunctivitis	2 (18.2)	0	0	0
Dyspnoea	1 (9.1)	7 (14.3)	1 (14.3)	4 (7.4)
Dyspepsia	1 (9.1)	6 (12.2)	0	2 (3.7)
Fatigue	1 (9.1)	6 (12.2)	2 (28.6)	4 (7.4)
Hypotension	1 (9.1)	6 (12.2)	0	4 (7.4)
Nausea	1 (9.1)	6 (12.2)	1 (14.3)	6 (11.1)
Peripheral oedema	1 (9.1)	5 (10.2)	0	2 (3.7)
Pruritus	1 (9.1)	4 (8.2)	2 (28.6)	3 (5.6)
Insomnia	1 (9.1)	2 (4.1)	1 (14.3)	1 (1.9)
Blood creatine phosphokinase increased	1 (9.1)	1 (2.0)	1 (14.3)	0
Paraesthesia	1 (9.1)	0	1 (14.3)	3 (5.6)
Anxiety	1 (9.1)	0	1 (14.3)	1 (1.9)

Muscular weakness	1 (9.1)	0	1 (14.3)	0
Diarrhoea	0	10 (20.4)	1 (14.3)	7 (13.0)
Cough	0	9 (18.4)	0	5 (9.3)
Palpitations	0	8 (16.3)	1 (14.3)	2 (3.7)
Nasopharyngitis	0	5 (10.2)	1 (14.3)	4 (7.4)
Peripheral swelling	0	5 (10.2)	1 (14.3)	4 (7.4)
Upper respiratory tract infection	0	4 (8.2)	1 (14.3)	7 (13.0)
Pain in extremity	0	4 (8.2)	1 (14.3)	1 (1.9)
Urinary tract infection	0	4 (8.2)	1 (14.3)	1 (1.9)
Constipation	0	3 (6.1)	1 (14.3)	3 (5.6)
Pyrexia	0	2 (4.1)	1 (14.3)	3 (5.6)
Musculoskeletal pain	0	2 (4.1)	1 (14.3)	2 (3.7)
Upper abdominal pain	0	2 (4.1)	1 (14.3)	1 (1.9)
Hot flush	0	2 (4.1)	1 (14.3)	0
Decreased appetite	0	1 (2.0)	1 (14.3)	2 (3.7)
Fall	0	1 (2.0)	1 (14.3)	2 (3.7)
Exertional dyspnoea	0	1 (2.0)	1 (14.3)	1 (1.9)
Pulmonary function test decreased	0	1 (2.0)	1 (14.3)	0
Weight increased	0	1 (2.0)	1 (14.3)	0
Sjögren’s syndrome	0	0	2 (28.6)	1 (1.9)
Hypertension	0	0	1 (14.3)	3 (5.6)
Depression	0	0	1 (14.3)	2 (3.7)
Weight decreased	0	0	1 (14.3)	2 (3.7)
Myositis	0	0	1 (14.3)	1 (1.9)
Pericarditis	0	0	1 (14.3)	1 (1.9)
Skin tightness	0	0	1 (14.3)	1 (1.9)
Arrhythmia	0	0	1 (14.3)	0
Ventricular tachycardia	0	0	1 (14.3)	0

Blepharitis	0	0	1 (14.3)	0
Cellulitis	0	0	1 (14.3)	0
Dermatomyositis	0	0	1 (14.3)	0
Increased upper airway secretion	0	0	1 (14.3)	0
Lip injury	0	0	1 (14.3)	0
Liver function test increased	0	0	1 (14.3)	0
Lower gastrointestinal haemorrhage	0	0	1 (14.3)	0
Peripheral neuropathy	0	0	1 (14.3)	0
Skin lesion	0	0	1 (14.3)	0
Syncope	0	0	1 (14.3)	0

Table shows adverse events reported in ⩾10% of patients in any group.

FVC%, forced vital capacity per cent predicted; ILD, interstitial lung disease.

Two patients (18.2%) with ILD receiving riociguat experienced an SAE: abdominal pain and intraductal proliferative breast lesion, each reported in 1 patient (9.1%). One patient (14.3%) with ILD receiving placebo experienced a total of three SAEs: pericarditis, syncope and ventricular tachycardia (incidence of each event: 14.3%).