Long-term extension results of RISE-SSc, a randomised, placebo-controlled trial of riociguat in patients with early diffuse cutaneous systemic sclerosis

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Keywords: systemic sclerosis; treatment outcomes; riociguat; interstitial lung disease

Summary

Background The phase 2b RIociguat Safety and Efficacy in patients with diffuse cutaneous Systemic Sclerosis (RISE-SSc) trial (ClinicalTrials.gov, NCT02283762) investigated riociguat *vs* placebo in early diffuse cutaneous systemic sclerosis (dcSSc). The long-term extension (LTE) evaluated safety and exploratory treatment effects for an additional year.

Methods Patients were enrolled between 15 January 2015 and 8 December 2016. Those who completed the 52-week, randomised, parallel-group, placebo-controlled, double-blind phase of RISE-SSc were eligible for the LTE. Patients originally randomised to riociguat continued therapy. Those originally randomised to placebo were switched to riociguat, adjusted up to 2·5 mg three times daily in a 10-week, double-blind dose-adjustment phase, followed by an open-label phase. Treatment effects assessed included modified Rodnan skin score (mRSS). Statistical analyses were descriptive. Safety including adverse events and serious adverse events was assessed in the long-term safety analysis set.

Findings In total, 87/121 (72%) patients in the main RISE-SSc study entered the LTE (riociguat→riociguat, n=42; placebo→riociguat, n=45). Overall, 82/87 patients (94%) in the LTE experienced an adverse event; most (n=66/87; 76%) were of mild to moderate severity, with no increase in pulmonary-related serious adverse events in patients with interstitial lung disease (ILD). Mean (95% confidence interval) mRSS scores decreased from week 52 to 112 by –2·6 (–4·4 to –0·9) points in the riociguat→riociguat group and –4·0 (–5·5 to –2·5) in the riociguat→placebo group.

Interpretation No new safety signals were observed with long-term riociguat in patients with dcSSc. Study limitations include the absence of a comparator group in this open-label extension study.

Funding Bayer AG and Merck Sharp & Dohme LLC.

Research in context

Evidence before this study

At the time RIociguat Safety and Efficacy in patients with diffuse cutaneous Systemic Sclerosis (RISE-SSc) was conceived (2018), no therapy had been proven to reverse the vascular and fibrotic damage in patients with scleroderma. Due to the high medical need, a number of drugs, such as methotrexate, mycophenolate mofetil, and cyclosporine, were in use off-label in an attempt to slow the progression of fibrosis. Current treatment options only targeted specific systemic sclerosis (SSc)-related manifestations. In the European Union, only bosentan was approved to reduce the number of new digital ulcers in patients with SSc and ongoing digital ulcer disease. The soluble guanylate cyclase stimulator riociguat had shown antifibrotic actions in skin and other tissues in in vitro and in vivo models and had demonstrated benefits in patients with pulmonary arterial hypertension (PAH), including PAH associated with SSc. Consequently, riociguat was investigated in the phase 2b, 52-week, randomised, double-blind, placebo-controlled RISE-SSc study in patients with diffuse cutaneous systemic sclerosis (dcSSc).

Added value of this study

The primary endpoint of RISE-SSc (reduction in modified Rodnan skin score [mRSS]) was not met (mean change from baseline –2·09 with riociguat *vs* –0·77 with placebo, p=0·08), but potential efficacy signals were seen. This open-label, long-term extension (LTE) study of RISE-SSc was therefore performed according to the trial protocol. No new safety signals were observed in patients with dcSSc receiving an additional year of riociguat therapy.

mRSS scores decreased numerically during the LTE in patients previously randomized to placebo and in those who continued riociguat. Digital ulcer burden was stable in patients who

previously received riociguat but continued to increase in those who previously received placebo, despite switching to riociguat.

Implications of all the available evidence

The LTE study results show that riociguat was well tolerated when given as long-term treatment. Further investigation of riociguat in larger cohorts of patients with dcSSc is warranted. Such studies could investigate riociguat as part of concurrent or sequential combinations with proven and/or commonly used therapies such as nintedanib, mycophenolate mofetil, or tocilizumab, in conjunction with patient profiling to select individualised therapy.

Introduction

Systemic sclerosis (SSc) is a severe, multiorgan autoimmune connective tissue disease characterised by extensive skin and internal organ fibrosis and vasculopathy.[1-3] SSc can seriously affect quality of life[3] and has high morbidity and mortality, particularly in patients with diffuse cutaneous SSc (dcSSc).[3, 4] Many drugs are used to treat organ manifestations of SSc,[3, 5] but the only approved therapies to modify the disease course are nintedanib[6] and tocilizumab[7] for interstitial lung disease (ILD) associated with SSc[8] (mycophenolate mofetil[9] being widely used although not approved). In addition, autologous haematopoietic stem cell transplantation is recommended for selected patients.[10] Several other targeted therapies are under development.[11]

In preclinical in vitro and in vivo animal studies, soluble guanylate cyclase (sGC) stimulators exhibited consistent anti-inflammatory, antifibrotic, and antiproliferative effects mediated partly by reduction of transforming growth factor beta-1 signalling.[12, 13] In the placebo-controlled, phase 3 Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator

Trial 1 (PATENT-1), the oral sGC stimulator riociguat improved functional capacity and pulmonary haemodynamics in adults with pulmonary arterial hypertension (PAH), including a subgroup with PAH associated with SSc, and was well tolerated.[14, 15] Additionally, riociguat improved digital blood flow in some patients with Raynaud's phenomenon in a single-dose pilot study.[16] Based on these observations, it was hypothesised that riociguat may reduce tissue fibrosis in dcSSc. It was therefore evaluated in the RIociguat Safety and Efficacy in patients with diffuse cutaneous Systemic Sclerosis (RISE-SSc) trial in patients with early dcSSc.[17]

While the study did not meet its primary endpoint of a significant decrease in modified Rodnan skin score (mRSS) at week 52, secondary exploratory analyses showed potential treatment effects of riociguat vs placebo, including a reduction in the development of digital ulcers.[17] To evaluate the safety and exploratory outcomes of longer-term treatment with riociguat, patients from RISE-SSc were eligible to enter a prespecified open-label long-term extension (LTE) in which all patients received riociguat. We assessed safety and outcomes in patients who were initially randomized to riociguat or placebo to determine if there was any effect of earlier riociguat initiation on these parameters.

Methods

Study design

RISE-SSc (ClinicalTrials.gov, NCT02283762) was a randomised, 52-week, double-blind, placebo-controlled, parallel-group, phase 2b, international, multicentre study conducted in 60 outpatient hospital centres in 15 countries (Australia, New Zealand, Canada, the USA, Belgium, the Czech Republic, France, Germany, Hungary, Italy, Switzerland, the United Kingdom, the Netherlands, Turkey, and Japan).[17] It ran from 15 January 2015 to 15

December 2017 and was completed according to protocol. Patients who completed the double-blind phase were eligible to enter the LTE in which patients originally randomised to riociguat continued therapy (the riociguat→riociguat group), while patients originally randomised to placebo were switched to oral riociguat (the placebo→riociguat group). The LTE was initially planned for up to 6 years after the end of the double-blind phase. However, as RISE-SSc did not meet its primary endpoint, the study was terminated early, with first patient first visit for the LTE on 8 February 2016 and last patient last visit on 28 March 2019.

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. All study data were regularly reviewed by an independent Data Monitoring Committee.

Patients

Eligible patients were ≥18 years of age and fulfilled American College of Rheumatology/European League Against Rheumatism criteria for dcSSc.[18] Patients were recruited by the principal investigator of each study centre. Full inclusion and exclusion criteria were published previously.[17] Patients with pulmonary hypertension as determined by right heart catheterisation were excluded from RISE-SSc to avoid depriving patients with PAH of the benefits of riociguat in this condition.[14, 15] All patients provided written informed consent.

Intervention assignment and procedures

Patients in the placebo→riociguat group were switched to riociguat (up to 2·5 mg three times daily) in the 10-week dose-adjustment phase (weeks 52–62). The riociguat→riociguat group continued treatment at the same dose while undergoing sham dose adjustment. Active riociguat and placebo tablets were identical in appearance and smell, and the packaging and labelling were designed to maintain blinded conditions for investigators and patients. After

the LTE dose-adjustment phase, riociguat treatment continued open-label until study termination, when patients entered the 30-day safety follow-up. Rescue medication (see online appendix p 2) was permitted from week 26 of the double-blind phase at investigator discretion, although concomitant nitrates, nitric oxide donors, and phosphodiesterase inhibitors (type 5 or non-specific) were not permitted.

Safety assessments continued throughout the LTE, with adverse event (AE) recording and evaluation of vital signs every 2 weeks during the dose-adjustment phase and every 12 weeks during the open-label phase. Efficacy outcome measures were assessed every 12 weeks from the start of the LTE (week 52). AEs, mRSS, pulmonary function tests, and patient-reported outcomes (PROs) were also assessed at the discontinuation visit. Digital ulcer burden was also evaluated during the dose-adjustment period of the LTE.

Outcomes

Safety assessments included evaluation of vital signs, AEs, and serious AEs (SAEs) coded by Medical Directory for Regulatory Activities (MedDRA) preferred terms. Based on previous experience with riociguat, symptomatic hypotension and serious haemoptysis were defined as AEs of special interest (AESIs). All patients underwent safety follow-up 30 [+5] days after the last dose of study medication (see online appendix p 2–3).

All outcome measures were exploratory in the LTE to RISE-SSc and were assessed from week 52 to week 112. Change in mRSS and the percentages of patients with mRSS worsening or improvement of ≥20%, 40%, or 60% were calculated, mRSS progression (worsening) being defined as an increase of either >5 units and ≥25% or >4 units and ≥20% from baseline,[19] and mRSS regression (improvement) as a decrease of >5 units and ≥25% from baseline. Pulmonary function was assessed with FVC (L), FVC %predicted, and

haemoglobin-corrected diffusing capacity of the lung for carbon monoxide (DL_{CO}). Pulmonary function was also assessed in patients with a medical history of ILD at baseline, defined according to MedDRA preferred terms 'interstitial lung disease' and 'pulmonary fibrosis'.

Worsening of end-organ disease was assessed, including cardiac, renal pulmonary, gastrointestinal, and digital ischaemia. Other exploratory endpoints included digital ulcer burden (see online appendix p 2). Quality of life was assessed using the Short Form 36 (SF-36), Scleroderma Health Assessment Questionnaire (S-HAQ; comprising the standard Health Assessment Questionnaire-Disability Index [HAQ-DI] and visual analogue scales [VASs]), University of California, Los Angeles, Scleroderma Clinical Trial Consortium Gastrointestinal Scale (UCLA SCTC GIT) 2·0,[20] and Patient-Reported Outcomes Measurement Information System (PROMIS)-29.

Statistical analyses

Statistical analyses were performed using SAS v9·2 software (SAS Institute Inc., Cary, Indiana, USA). All analyses in the LTE were conducted on the long-term safety analysis set, defined as all patients randomised and treated with study medication in the double-blind phase who continued study medication in the LTE. Data were summarised descriptively by treatment group. The number of data available and missing data, mean, standard deviation, minimum, median, quartiles (if data were clearly non-normal) and maximum were calculated for continuous data. Two-sided confidence intervals were also calculated for changes from week 52 to 112 in mRSS and pulmonary function. Frequency tables were generated for categorical data. mRSS and pulmonary function were evaluated every 12 weeks during open-label therapy and at the final visit. All variables are presented as observed values with no

imputation for missing data. Mean changes were obtained by first calculating the individual change from baseline for each visit and then averaging all changes at each visit. The study protocol and statistical analyses plans are available at [[URL to be confirmed on acceptance]].

Patient and public involvement

This study did not have patient or public involvement in its design, participant recruitment, or conduct, although PROs were included as exploratory endpoints.

Role of the funding source

Bayer AG designed the study in collaboration with the authors. MW and FK of Bayer AG analysed and interpreted the study results, led post hoc analysis generation, and, along with all other authors, revised the manuscript and approved the final draft for publication.

Results

Of 121 patients enrolled between 15 January 2015 and 8 December 2016 and initially randomised in RISE-SSc (riociguat, n=60; placebo, n=61), 88 completed the double-blind phase (riociguat, n=42; placebo, n=46) (figure 1). One patient in the placebo arm declined to enter the LTE; consequently, 87 patients were included in the analysis. The LTE phase was completed with at least 112 weeks' follow-up by 32 patients originally randomised to riociguat (riociguat→riociguat) and 31 patients originally randomised to placebo. Ten of 42 patients in the riociguat→riociguat group (24% of those entering the LTE) and 14 of 45 in the

placebo→riociguat group (31% of those entering the LTE) discontinued treatment and entered the safety follow-up. The most common reasons for discontinuation were patient withdrawal in the riociguat→riociguat group and AEs in the placebo→riociguat group (figure 1).

The combined mean (SD) duration of riociguat exposure in the double-blind and LTE phases was 1061 (259) days in the riociguat→riociguat group and 596 (302) days in the placebo→riociguat group. The median (interquartile range [IQR]) duration of follow-up was 1118.5 (890–1323) and 1037 (789–1242) days, respectively. The median (IQR) treatment duration was 1092 (855–1288) and 649 days, respectively. Overall cumulative riociguat exposure was 195·4 person-years (riociguat→riociguat, 122·0 person-years; placebo→riociguat, 73·4 person-years).

Baseline characteristics of the overall population at study entry and for the riociguat→riociguat and placebo→riociguat groups at the start of the LTE are shown in table 1. Both groups included 11 patients with ILD by medical history, whereas by high-resolution computed tomography (HRCT) performed as part of clinical care before the randomization, ILD was present in 12 riociguat→riociguat patients (29%) and nine placebo→riociguat patients (20%). Demographics and disease characteristics at the initial double-blind baseline in patients who entered the LTE were generally well balanced between treatment groups (online appendix p 3–4).

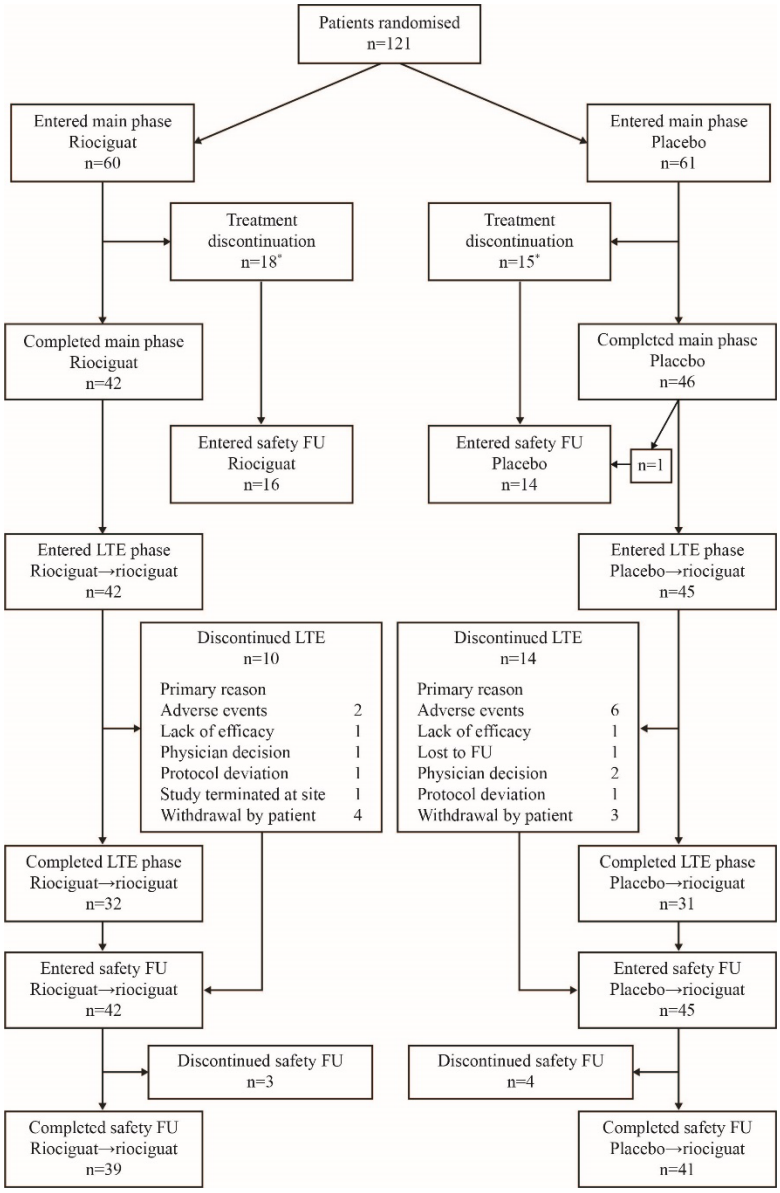


Figure 1: **Patient disposition**

FU=follow-up. LTE=long-term extension. * In the main study, 2 patients in the riociguat group and 2 patients in the placebo group completed safety FU but did not complete case report forms, and therefore they are not counted as entering safety FU in the main study. One patient in the placebo group completing the main treatment phase did not enter the LTE phase and entered and completed the safety FU.

	Double-blind baseline (n=121)	Riociguat→riociguat (n=42)	Placebo→riociguat (n=45)
Age, years	51 (12)	52 (12)	49 (13)
Female sex, n (%)	92 (76)	31 (74)	34 (76)
Male sex, n (%)	29 (24)	11 (26)	11 (24)
Race, n (%)			
White	89 (74)	28 (67)	34 (76)
Black	5 (4)	0 (0)	1 (2)
Asian	24 (20)	11 (26)	10 (22)
Other or not reported	3 (2)	3 (7)	0 (0)
Disease duration, months	9·0 (6·4)	8·9 (7·8)[†]	8·9 (5·8)
Median (IQR)	8·2 (3·7–13·4)	7·2 (0·5–44·4)	8·7 (0·7–18·4)
mRSS	16·8 (3·7)	14·1 (5·8)	15·6 (10·1)
ILD by medical history, n (%)	25 (21)	11 (26)	11 (24)
FVC %predicted	93 (18)	90 (19)	93 (15)[*]
DL_{CO} (mmol/min/kPa)			
Overall	6.04 (1.97)	5·79 (1·92)	5·88 (1·84)
DL_{CO} %predicted (haemoglobin corrected)	76 (19)	77 (21)	74 (19)
Swollen joint count	2·0 (4·7)	1·9 (4·8)	0·8 (2·8)
Median (IQR)	0 (0–2)	0 (0–0)	0 (0–0)
Swollen joint count ≥1, n (%)	38 (31)	8 (19)	7 (16)
Tender joint count	3·0 (6·2)	2·8 (6·1)	1·1 (3·8)
Median (IQR)	0·5 (0–3·5)	0 (0–1)	0 (0–0)
Tender joint count ≥1, n (%)	51 (42)	13 (31)	8 (18)
Tendon friction rubs		..	..
Tendon friction rubs ≥1, n (%)	35 (29)	0 (0)	0 (0)
Digital ulcer count	0·3 (1·1)	0·0 (0·3)	0·2 (0·7)
Median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)
Digital ulcer count ≥1, n (%)	15 (12)	1 (2)	4 (9)
Mean HAQ-DI, units	0·8 (0·7)	0·8 (0·7)	0·8 (0·8)
Median (range)	0.8 (0–2.4)	0·6 (0–2·4)	0·6 (0–2·8)
Anti-Scl-70 (anti-topoisomerase I) positive, n (%)	49 (40)	17 (40)	16 (36)
Anti-RNA polymerase III positive, n (%)[‡]	26 (21)	9 (21)	11 (24)
Anti-centromere-B positive, n (%)	10 (8)	3 (7)	3 (7)[*]

Table 1: **Patient demographics and disease characteristics at the LTE baseline (week 52) and full study population at double-blind baseline**

All data are mean (SD), unless otherwise specified. DL_{CO}=diffusing capacity of the lung for carbon monoxide. FVC=forced vital capacity. HAQ-DI=Health Assessment Questionnaire-Disability Index. ILD=interstitial lung disease. LTE=long-term extension. mRSS=modified Rodnan skin score. RNA=ribonucleic acid. SD=standard deviation. [*]n=44. [†]n=41. [‡]Blood samples for autoantibody screen were only conducted at baseline to the randomised phase at the start of the study.

Overall, 82 of the 87 patients (94%) experienced an AE during the LTE; most AEs were mild to moderate in severity (table 2).

	Week 52 to end of LTE			Baseline to end of LTE		
	Riociguat→riociguat (n=42)	**Placebo→riociguat (n=45)**	**Total (n=87)**	**Riociguat→riociguat (n=42)**	**Placebo→riociguat (n=45)**	**Total (n=87)**
AEs, n (%)	**40 (95)**	**42 (93)**	**82 (94)**	**41 (98)**	**42 (93)**	**83 (95)**
Study drug-related* AEs	17 (40)	25 (56)	42 (48)	33 (79)	30 (67)	63 (72)
Discontinuation of study drug due to AE	2 (5)	6 (13)	8 (9)	2 (5)	7 (16)	9 (10)
Maximum intensity for any AE, n (%)						
Mild	14 (33)	11 (24)	25 (29)	9 (21)	9 (20)	18 (21)
Moderate	17 (40)	24 (53)	41 (47)	21 (50)	22 (49)	43 (49)
Severe	9 (21)	7 (16)	16 (18)	11 (26)	11 (24)	22 (25)
Maximum intensity for study drug-related* AE, n (%)						
Mild	13 (31)	11 (24)	24 (28)	24 (57)	12 (27)	36 (41)
Moderate	3 (7)	12 (27)	15 (17)	8 (19)	13 (29)	21 (24)
Severe	1 (2)	2 (4)	3 (3)	1 (2)	5 (11)	6 (7)
SAEs, n (%)	**10 (24)**	**11 (24)**	**21 (24)**	**12 (29)**	**17 (38)**	**29 (33)**
Study drug-related* SAEs	1 (2)	3 (7)	4 (5)	1 (2)	5 (11)	6 (7)
Discontinuation of study drug due to SAE	1 (2)	3 (7)	4 (5)	1 (2)	4 (9)	5 (6)
Most frequent AEs, n (%)†						
Nasopharyngitis	11 (26)	10 (22)	21 (24)	13 (31)	14 (31)	27 (31)
GORD	7 (17)	8 (18)	15 (17)	19 (45)	13 (29)	32 (37)
Upper RTI	7 (17)	6 (13)	13 (15)	9 (21)	11 (24)	20 (23)
Vomiting	7 (17)	4 (9)	11 (13)	10 (24)	5 (11)	15 (17)
Cough	6 (14)	3 (7)	9 (10)	9 (21)	6 (13)	15 (17)

Skin ulcer	6 (14)	4 (9)	10 (11)	9 (21)	9 (20)	18 (21)
Bronchitis	5 (12)	0 (0)	5 (6)	8 (19)	1 (2)	9 (10)
Diarrhoea	5 (12)	8 (18)	13 (15)	9 (21)	12 (27)	21 (24)
Hypotension‡	5 (12)	7 (16)	12 (14)	11 (26)	9 (20)	20 (23)
Interstitial lung disease	5 (12)	5 (11)	10 (11)	7 (17)	6 (13)	13 (15)
Arthralgia	4 (10)	6 (13)	10 (11)	10 (24)	14 (31)	24 (28)
Constipation	4 (10)	2 (4)	6 (7)	5 (12)	6 (13)	11 (13)
Myalgia	4 (10)	2 (4)	6 (7)	5 (12)	4 (9)	9 (10)
Pain in extremity	4 (10)	2 (4)	6 (7)	7 (17)	3 (7)	10 (11)
Nausea	2 (5)	6 (13)	8 (9)	4 (10)	10 (22)	14 (16)
Dizziness	3 (7)	6 (13)	9 (10)	11 (26)	11 (24)	22 (25)
Palpitations	3 (7)	1 (2)	4 (5)	8 (19)	4 (9)	12 (14)
Epistaxis	3 (7)	1 (2)	4 (5)	5 (12)	3 (7)	8 (9)
Anaemia	3 (7)	4 (9)	7 (8)	3 (7)	5 (11)	8 (9)
Influenza	3 (7)	4 (9)	7 (8)	5 (12)	4 (9)	9 (10)
Headache	3 (7)	4 (9)	7 (8)	9 (21)	12 (27)	21 (24)
Gastroenteritis	3 (7)	5 (11)	8 (9)	4 (10)	5 (11)	9 (10)
Dyspnoea	3 (7)	3 (7)	6 (7)	6 (14)	4 (9)	10 (11)
Abdominal pain	3 (7)	1 (2)	4 (5)	5 (12)	3 (7)	8 (9)
Raynaud’s phenomenon	2 (5)	2 (4)	4 (5)	5 (12)	4 (9)	9 (10)
Abdominal distension	1 (2)	4 (9)	5 (6)	4 (10)	5 (11)	9 (10)
Peripheral oedema	1 (2)	3 (7)	4 (5)	5 (12)	5 (11)	10 (11)
Dyspepsia	1 (2)	2 (4)	3 (3)	5 (12)	3 (7)	8 (9)

Pruritus	1 (2)	0	1 (1)	3 (7)	5 (11)	8 (9)
Fatigue	0	4 (9)	4 (5)	5 (12)	9 (20)	14 (16)
Peripheral swelling	0	0	0	5 (12)	4 (9)	9 (10)
AEs of special interest, n (%)						
Symptomatic hypotension[§]	5 (12)	4 (9)	9 (10)	4 (10)	6 (13)	10 (11)
Serious haemoptysis	0	0	0	0	0	0

***Table 2*: Summary of AEs from baseline to the end of the LTE (week 112) and from week 52 to the end of the LTE (week 112)**

Data are reported for AEs that started or worsened after first administration of study drug up to 2 days after end of treatment with study drug. AE=adverse event. LTE=long-term extension. GORD=gastro-oesophageal reflux disease. SAE=serious AE. [*]Analyses of drug-related AEs were based on the assessment of causal relationship to study medication as determined by the investigator. [†]Occurring in ≥10% of patients in either treatment group. [‡]Refers to both symptomatic and asymptomatic hypotension. [§]Included hypotension as a preferred term in two patients (5%) in the riociguat→riociguat group and four (9%) in the placebo→riociguat group.

The most frequently reported AEs during the LTE were nasopharyngitis (n=21/87; 24%), gastro-oesophageal reflux disease (GORD) (n=15/87; 17%), upper respiratory tract infection (n=13/87; 15%), and diarrhoea (n=13/87; 15%) (table 2). Two of 42 patients (5%) in the riociguat→riociguat group and six of 45 (13%) in the placebo→riociguat group discontinued the study due to an AE. No AE resulting in discontinuation was reported in more than one patient (online appendix p 5). Symptomatic hypotension (dizziness, headache, or hypotension) was reported in five of 42 patients (12%) in the riociguat→riociguat group and four of 45 (9%) in the placebo→riociguat group (table 2 and online appendix p 5). No serious haemoptysis events were reported. AEs considered by the investigator to be related to riociguat treatment were reported in 17/42 patients (40%) in the riociguat→riociguat group and 25/45 patients (56%) in the placebo→riociguat group. The most frequently occurring treatment-related AEs were hypotension (riociguat→riociguat, 3/42 [7%]; placebo→riociguat, 7/45 [16%]), dizziness (3/42 [7%] and 4/45 [9%], respectively), diarrhoea (1/42 [2%] and 4/45 [9%]), headache (1/42 [2%] and 4/45 [9%]) and nausea (0/42 [0%] and 5/45 [11%]), respectively (online appendix p 6).

During the LTE, SAEs were reported in ten of 42 patients (24%) in the riociguat→riociguat group and 11 of 45 patients (24%) in the placebo→riociguat group. SAEs considered by the investigator to be related to riociguat were reported in one of 42 patients (2%) in the riociguat→riociguat group (osteolysis) and three of 45 patients (7%) in the placebo→riociguat group (one patient each with fluid overload and cardiac failure, and one patient with tachycardia and ileus). In the riociguat→riociguat group, one of 42 patients (2%) experienced serious acute respiratory distress syndrome and one patient (2%) experienced serious epistaxis. No respiratory SAEs were reported in the placebo→riociguat group.

No deaths were reported during the LTE, and there were no AEs or SAEs related to procedures required by the study protocol during the study.

Rates of most AEs and SAEs from baseline to the end of LTE were higher than during the LTE, as expected from the longer observation period. The most common AEs were GORD (n=32/87; 37%), nasopharyngitis (n=27/87; 31%), arthralgia (n=24/87; 28%), and dizziness (n=22/87; 25%).

Safety outcomes in male and female patients are shown in the online appendix (p 7).

Safety in patients with ILD by medical history at baseline was generally similar to that observed in patients without ILD (online appendix p 8–9), and the risk of any SAEs in patients with ILD (n=5/22 [23%] overall) was similar to the main study population. No pulmonary SAEs were reported. Respiratory AEs, however, were more common in patients with ILD *vs* no ILD (online appendix p 10–11).

I The time course of change in mRSS is shown in figure 2. From week 52 to 112 there were mean changes of –4·0 (95% CI –5·5 to –2·5) and –2·6 (95% CI –4·4 to –0·9) in the placebo→riociguat and riociguat→riociguat groups, respectively.

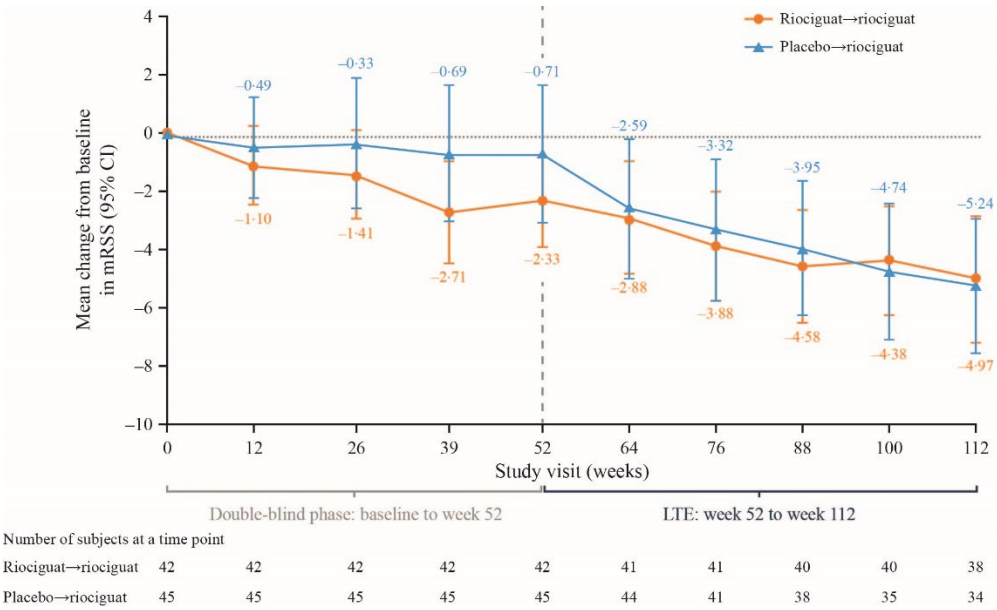


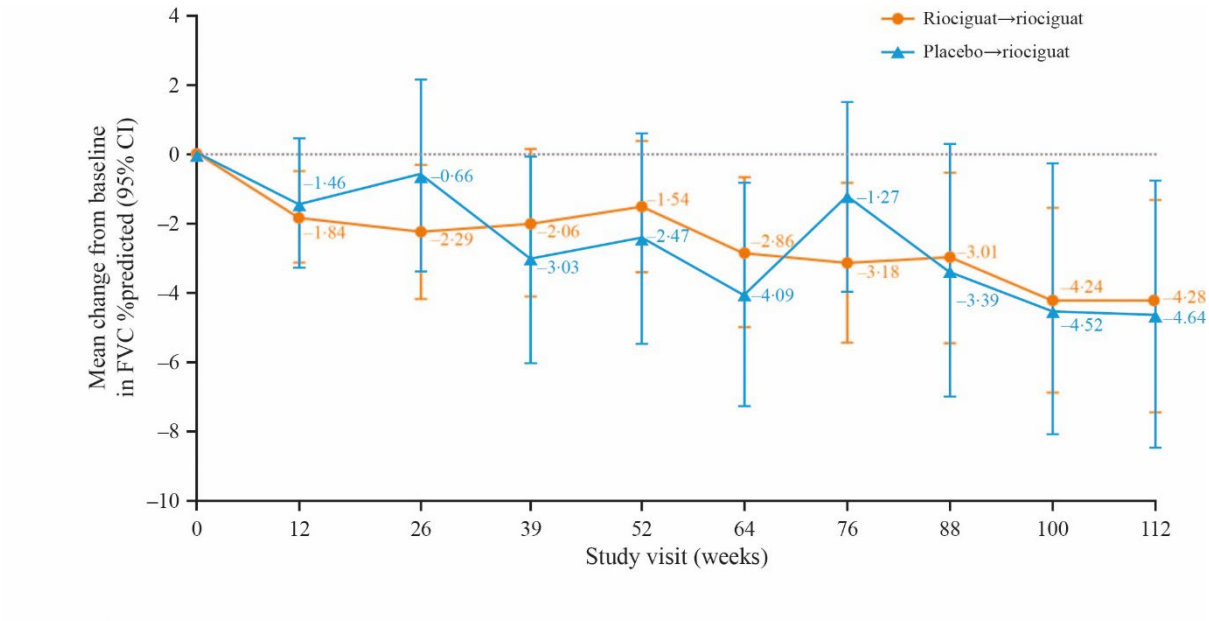
Figure 2: **Mean (95% CI) change in mRSS from baseline to week 112**

CI=confidence interval. LTE=long-term extension. mRSS=modified Rodnan skin score.

From week 52 to week 112, 24% of patients in both LTE groups (nine of 38 in the riociguat→riociguat group and eight of 34 in the placebo→riociguat group) experienced an improvement in mRSS score (>5 units and ≥25% decrease) and no patients in either group showed worsening (>5 units and ≥25% increase). This was different from the double-blind phase in which, from week 0 to week 52, 23/42 patients (55%) in the riociguat→riociguat group and 15/45 patients (33%) in the placebo→riociguat group experienced improvement in mRSS score and 7/42 (17%) and 13/45 (29%), respectively, experienced worsening. The proportions of patients with an increase or decrease of ≥20%, ≥40%, or ≥60% in mRSS score are shown in online appendix p 13. As assessment of the mRSS is partly subjective,[1] these results should be viewed with caution. Also, given the low baseline mRSS, a small absolute change would represent a relatively large percentage value.

The time course of change in FVC %predicted is shown in figure 3. In placebo→riociguat and riociguat→riociguat patients, the mean (95% CI) change in FVC %predicted from week

52 to 112 was –1·6 (–8.5 to –0.8) and –3·0 (–7.2 to –1.4), respectively. Changes in FVC and DL_{CO} in overall and in patients with ILD are described in the online appendix, p 14–15.



Number of subjects at a time point

Riociguat→riociguat	42	40	41	42	42	41	41	39	39	36
Placebo→riociguat	45	45	45	45	44	44	41	38	35	34

Figure 3: Mean (95% CI) change in FVC %predicted from baseline to week 112 in the long-term safety analysis set

CI=confidence interval. FVC=forced vital capacity. LTE=long-term extension.

PROs were assessed throughout the LTE. Changes in PRO scores from baseline to week 52 and from week 52 to 112 were generally small, with large variations between patients (online appendix p 16–22). Changes in UCLA SCTC GIT scores from week 52 to week 112 were mean (SD) 0.05 (0.29) (median, 0.00; range –0.56 to 1.123 for riociguat→riociguat (n=37) and mean (SD) 0.05 (0.17) (median, 0.01; range –0.21 to 0.56 for placebo→riociguat (n=34).

Worsening of end-organ disease from week 52 to week 112 was observed in one of 42 patients (2%) in the riociguat→riociguat group (arrhythmias and/or conduction defects

requiring treatment) and two of 45 patients (4%) in the placebo→riociguat treatment group (arrhythmias and/or conduction defects requiring treatment [n=1] and worsening of gastrointestinal disease requiring hospitalisation [n=1]). From week 52 to week 112, three of 42 riociguat→riociguat patients (7%) required new rescue therapy with methotrexate, and three (7%) required mycophenolate mofetil. Two of 42 placebo→riociguat patients (5%) required rescue therapy with mycophenolate mofetil. Concomitant medications from week 52 to the end of the study are shown in online appendix p 23. Apart from one patient in the riociguat→riociguat group who received tadalafil due to Raynaud's disease and two patients who received glycerol nitrate due to subcutaneous calcification of the right thumb and arterial hypertension, patients received vasodilators after the last dose of riociguat and so these were not considered protocol-prohibited medications.

In the riociguat→riociguat group, four of 42 patients (10%) developed new digital ulcers during the double-blind phase, and a further five (12%) developed new digital ulcers in the LTE (figure 4A). In the placebo→riociguat group, 9/45 patients (20%) developed new digital ulcers in the double-blind phase and 2/45 (4%) did so in the LTE (figure 4A). In the riociguat→riociguat group, there were nine new digital ulcers at week 52 and 17 at week 112, respectively, while in the placebo→riociguat group there were 64 and 129 new digital ulcers, respectively (figure 4B).

The change in digital ulcer net burden from week 52 to last visit was –0·024 in the riociguat→riociguat group and +0·222 in the placebo→riociguat group. Within this time frame, five of 42 patients (12%) in the riociguat→riociguat group and 11/45 patients (24%) in the placebo→riociguat group received dermatological agents for the treatment of wounds and ulcers. Between week 52 and study end, calcium channel blockers were used in

12/42 patients (29%) in the riociguat→riociguat group and eight of 45 patients (18%) in the placebo→riociguat group.

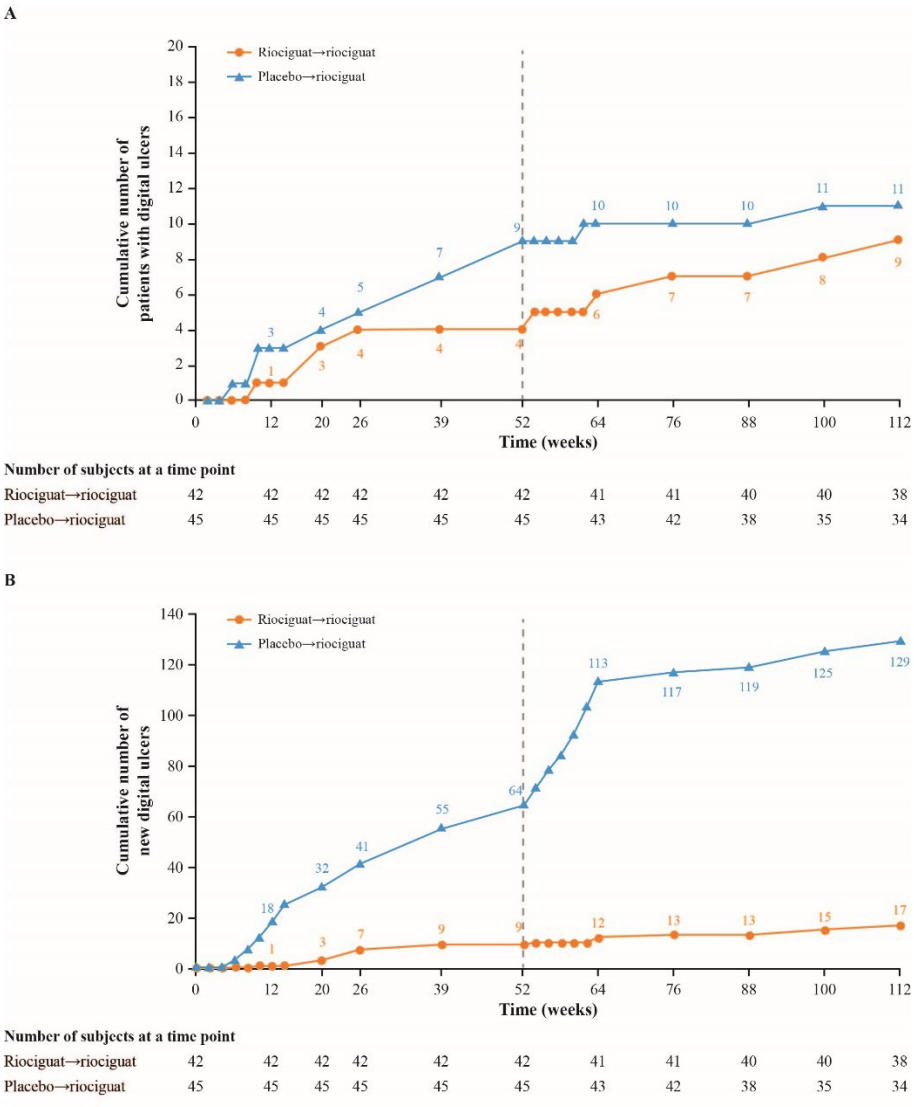


Figure 4: **Cumulative numbers of patients with new digital ulcers (A) and cumulative numbers of new digital ulcers (B) from baseline to week 112**

Discussion

This open-label LTE of the randomised, placebo-controlled, double-blind RISE-SSc study of riociguat in patients with dcSSc[17] revealed no new safety signals during long-term use of riociguat overall or in patients with ILD at baseline. Safety was consistent with the RISE-SSc double-blind phase,[17] the PATENT-1 and -2 studies in PAH,[15, 21] and the Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial (CHEST)-1 and -2 studies in chronic thromboembolic pulmonary hypertension.[22, 23] In general, observed AEs were either common adverse reactions for riociguat in its approved indications or known symptoms of dcSSc. AEs considered by the investigator to be related to riociguat occurred in more patients in the placebo→riociguat group than the riociguat→riociguat group, which is not unexpected, as patients who experienced riociguat-related AEs in the double-blind study were more likely to have discontinued before entering the LTE.

Lung function continued to decline in both groups during the study, although the rate of decline in FVC %predicted became slower in patients with ILD who switched to riociguat after receiving placebo. These results may suggest a beneficial role for riociguat in patients with ILD that warrants further investigation, although the sample size was small. No patient with ILD experienced pulmonary SAEs, in contrast with the Riociguat in Patients with Symptomatic Pulmonary Hypertension Associated with Idiopathic Interstitial Pneumonias (RISE-IIP) study of riociguat in pulmonary hypertension associated with idiopathic interstitial pneumonias, in which SAEs including worsening of ILD were reported.[24, 25] In patients with SSc-related ILD, mycophenolate mofetil and stem-cell transplantation [26] have been reported to improve FVC %predicted *vs* baseline,[9] nintedanib slows the decline in FVC,[6] and tocilizumab appears to stabilise this parameter compared to more rapid

progression under placebo,[7] although profiles of the patients enrolled in those trials were different from those in RISE-SSc, in terms of inclusion of limited cutaneous SSc, SSc duration, severity of ILD, and elevation of inflammatory markers. However, riociguat monotherapy is not adequate for treatment of ILD, and there remains a significant unmet clinical need for improved treatments for SSc.

From week 52 to week 112 the net burden of digital ulcers was stable in the riociguat→riociguat group but worsened in the placebo→riociguat group, and the cumulative number of new digital ulcers increased markedly in the latter group. These observations are inconsistent with the signal seen during the double-blind phase, in which riociguat was associated with fewer patients developing new digital ulcers and a lower cumulative number of new digital ulcers compared with placebo. A history of digital ulcers is a risk factor for the development of subsequent ulcers,[27] and patients in the placebo→riociguat group had developed more ulcers during the placebo-controlled period. This may partly explain why patients who switched to riociguat after 52 weeks of placebo did not see the same benefit as those who received riociguat from the start of the double-blind phase. The increase in the cumulative number of new digital ulcers in the placebo→riociguat group was particularly steep during the riociguat dose-adjustment phase (weeks 52–64). This may partly have been related to more vigilant assessment during this time. Digital ulcer burden includes other variables in addition to the number of ulcers and so it may not correlate closely with ulcer numbers.

The need for a long treatment duration was observed in a randomised study in patients with SSc-related digital ulcers where riociguat did not reduce the digital ulcer net burden relative

to placebo at 16 weeks but patients had complete healing of digital ulcers in the 16-week extension phase.[28] This highlights the importance of early treatment of vasculopathy and ulcer prevention in patients with dcSSc. Digital ulcers can also be considered as a safety concern during trials in patients with SSc, but safety analyses in the LTE showed no signal for excess DU with riociguat. Ulcers can also be assessed in terms of concomitant medication required to treat them. During the LTE, except for the contraindicated nitrates or nitric oxide donors and phosphodiesterase type 5 inhibitors, the addition of any other concomitant medication was at the discretion of the investigator, and more patients in the placebo→riociguat group received dermatological agents for the treatment of wounds and ulcers. RISE-SSc was not, however, designed to assess impact of riociguat treatment on ulcer evolution.

Limitations of this LTE include its open-label design, meaning that there was no placebo comparator. Its primary purpose was to assess the safety of riociguat, and all other endpoints were exploratory. Our analyses include relatively small numbers of patients, particularly in the ILD subgroups, and lack longer-term data. Consequently, no conclusions regarding the efficacy of riociguat can be made. In addition, the high rate of withdrawal (63 patients of the original trial cohort of 121 completed the LTE) may have biased the results in favour of patients with a good response to riociguat. Per-protocol assessments could lead to selection bias because of exclusion of patients with a poor response or who discontinue treatment as a result of AEs. Our use of MedDRA preferred terms to identify ILD is not as accurate as performing HRCT, which is the central diagnostic technique for ILD.[29, 30] Additionally, the results might not be generalisable to patients outside the study population (eg, advanced dcSSc or limited cutaneous SSc). Also, Raynaud's attacks were not evaluated during the LTE.

In summary, no new safety signals were observed in this long-term study of patients with dcSSc receiving riociguat. Future trials of riociguat or similar agents should explore if targeting vasculopathy and fibrosis by this mechanism of action, in combination with immunomodulatory agents, will have beneficial effects in SSc.

Contributors

DK and OD directly accessed and verified the underlying data reported in this manuscript and made the final decision to submit the manuscript for publication. KL worked with Bayer AG as an external statistician. MW and FK analysed and interpreted the results and led post hoc analysis generation. DK, OD, YA, CPD, MK, MM-C, JEP, TA, RB, LC, EH, TI, OI, SRJ, EDL, CS, VR, ES, RMS, VSm, VSt, WS, GS, and M-ET recruited and monitored patients and collected study data. All authors had full access to the data in the study, revised the manuscript, approved the final draft for submission, and take responsibility for submission.

Declaration of interests

OD has/had consultancy relationships with and/or has received research funding from, or has served as a speaker in the area of potential treatments for systemic sclerosis and its complications in the last 3 years for AbbVie, Acceleron, Amgen, AnaMar, Arxx Therapeutics, Baecon, Bayer AG, Blade, Boehringer Ingelheim, ChemomAb, Corbus, CSL Behring, Galapagos NV, GlaxoSmithKline, Glenmark, Horizon (Curzion), Inventiva, iQvia, Italfarmaco, Kymera, Medac, Medscape, Merck Sharp & Dohme, Mitsubishi Tanabe, Novartis, Pfizer, Roche, Roivant, Sanofi, Serodapharm, Target Bioscience AG, Topadur, and

UCB. OD is named on a patent issued for ‘mir-29 for the treatment of systemic sclerosis’ (US8247389, EP2331143).

YA reports personal fees from Actelion, Bayer AG, and Boehringer Ingelheim; grants and personal fees from Bristol Myers Squibb; and grants from Inventiva, Roche, and Sanofi, outside the submitted work.

CPD reports grants and personal fees from Arxx Therapeutics, CSL Behring, GlaxoSmithKline, and Inventiva; grants from Servier; and personal fees from Acceleron, Bayer AG, Corbus, Galapagos, Horizon, Roche, and Sanofi Aventis.

MK reports grants and personal fees from Boehringer Ingelheim, MBL, and Ono Pharmaceuticals; and personal fees from AbbVie, Asahi Kasei Pharma, Bayer AG, Chugai Pharmaceutical, Corbus, GlaxoSmithKline, Horizon, Janssen, Mitsubishi Tanabe, Mochida, and Nippon Shinyaku, outside the submitted work.

MM-C has received consulting fees or honoraria from Acceleron, Actelion, Bayer AG, Biogen, Boehringer Ingelheim, Chemomab, Corbus, CSL Behring, Galapagos, Inventiva, Janssen, Lilly, Mitsubishi, MSD, Pfizer, Regeneron, Roche, and Samsung.

JEP reports personal fees from AbbVie, Actelion, Amgen, Bayer AG, Bristol Myers Squibb, Lilly Pharmaceutical, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Sandoz, Sanofi, and UCB, outside the submitted work.

TA reports grants and personal fees from Astellas, Chugai, Daiichi-Sankyo, Mitsubishi Tanabe, Pfizer, and Takeda; grants from Alexion, Asahi Kasei, Bayer AG, Bristol Myers Squibb, Eisai, Otuska, and Takeda; and personal fees from Lilly, Ono Pharmaceutical, and Sanofi, outside the submitted work.

LC reports personal fees from Actelion, Bayer AG, Boehringer Ingelheim, Lilly, Medac, Novartis, Pfizer, and Roche-Genentech, outside the submitted work.

EH reports grants and personal fees from Actelion and GlaxoSmithKline; and personal fees from Boehringer Ingelheim, Roche, and Sanofi-Genzyme.

TI reports personal fees from AbbVie, Asahi Kasei Pharma, Astellas, Ayumi Pharmaceutical, Bristol Myers Squibb, Chugai Pharmaceutical, Daiichi-Sankyo, Eisai, Janssen, Mitsubishi Tanabe, Ono Pharmaceutical, Pfizer, and Sanofi, outside the submitted work.

SRJ was a site investigator for trials sponsored by Boehringer Ingelheim and Corbus; and served on advisory boards sponsored by Boehringer Ingelheim and Ikaria, Inc.

EDL reports consultancy relationships with Boehringer Ingelheim.

RB, OI, CS, and VR declare no competing interests.

ES has received grants and research support from Bayer AG.

RMS has received research funding from Boehringer Ingelheim; and has served as a consultant for Boehringer Ingelheim, Corbus, Forbius, and Medtelligence.

VSm reports grant/research support from the Belgian Fund for Scientific Research (FWRO), Boehringer Ingelheim Pharma GmbH & Co., Janssen-Cilag NV, and the Research Foundation Flanders (FWO); consultancy for Boehringer Ingelheim Pharma GmbH & Co., and Janssen-Cilag NV; and speaker fees from Actelion, Boehringer Ingelheim Pharma GmbH & Co., Janssen-Cilag NV, and UCB.

VSt reports participation in advisory boards, consultancy for economics of scleroderma management, and clinical trials for Bayer AG; investigator-initiated grants, advisory boards, and steering committees (consulting) for CSL Behring; participation in advisory boards and site primary investigator (PI) of clinical trials for Roche; site PI of clinical trials for the Immune Tolerance Network and Sanofi; and DSMB for open labs phase 2 trial and site PI for phase 3 trial for Corbus.

WS reports speaker fees, advisory board fees, and research grants from Janssen; advisory board fees from Boehringer Ingelheim; and research grants from GlaxoSmithKline.

GS reports personal fees from Berlin-Chemie/A. Menarini, Boehringer Ingelheim, CSL Behring, Janssen-Cilag, Eli Lilly, Novartis, Pfizer, Roche-Genentech, and Sager Pharma, outside the submitted work.

M-ET has/had consultancy relationships with and/or has received research funding from or has served as a speaker in the area of potential treatments for systemic sclerosis and its complications in the last 3 years for Boehringer Ingelheim, Gilead Galapagos, Glenmark, Lilly, and Medac.

MW is an employee of Bayer AG.

KL was an employee of StanFinn Oy, which was partly insourced to Bayer AG during the conduct of the trial and is now an employee of Bayer Oy.

FK is an employee of and holds stock/shares in Bayer AG.

DK reports personal fees from Acceleron, Actelion, Boehringer Ingelheim, Corbus, CSL Behring, Roche-Genentech, Horizon, Mitsubishi Tanabe Pharma, and Talaris Therapeutics; and is Chief Medical Officer of Eicos Sciences, Inc, a subsidiary of CiviBioPharma, where he has stock options.

Data sharing

Availability of the data underlying this publication will be determined according to Bayer's commitment to the European Federation of Pharmaceutical Industries and Associations and Pharmaceutical Research and Manufacturers of America principles for responsible clinical trial data sharing, pertaining to scope, time point, and process of data access. Bayer commits

to sharing upon request from qualified scientific and medical researchers, patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the USA and European Union as necessary for doing legitimate research. This commitment applies to data on new medicines and indications that have been approved by the European Union and US regulatory agencies on or after 1 January 2014. Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymised patient-level data and supporting documents from clinical studies to do further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the study sponsors section of the portal. Data access will be granted to anonymised patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

Acknowledgements

The study was jointly funded by Bayer AG and Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, New Jersey, USA. The authors thank the investigators and patients in the RISE-SSc trial, as well as the Data Monitoring Committee and the Central Adjudication Committee.

Medical writing services, provided by Richard Murphy PhD, of Adelphi Communications Ltd, Macclesfield, UK, were funded by Bayer AG, Berlin, Germany in accordance with Good Publication Practice 2022 guidelines.

References

1. Khanna, D., et al., *Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis.* J Scleroderma Relat Disord, 2017. **2**(1): p. 11-18.
2. Nagaraja, V., et al., *Current and future outlook on disease modification and defining low disease activity in systemic sclerosis.* Arthritis Rheum, 2020. **72**(7): p. 1049-1058.
3. Denton, C.P. and D. Khanna, *Systemic sclerosis.* Lancet, 2017. **390**(10103): p. 1685-1699.
4. Jaeger, V.K., et al., *Incidences and Risk Factors of Organ Manifestations in the Early Course of Systemic Sclerosis: A Longitudinal EUSTAR Study.* PLoS One, 2016. **11**(10): p. e0163894.
5. Denton, C.P., et al., *BSR and BHPR guideline for the treatment of systemic sclerosis.* Rheumatology (Oxford), 2016. **55**(10): p. 1906-1910.
6. Distler, O., et al., *Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease.* N Engl J Med, 2019. **380**(26): p. 2518-2528.
7. Khanna, D., et al., *Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial.* Lancet Respir Med, 2020. **8**(10): p. 963-974.
8. Khanna, D., et al., *Systemic Sclerosis-Associated Interstitial Lung Disease: How to Incorporate Two Food and Drug Administration-Approved Therapies in Clinical Practice.* Arthritis Rheumatol, 2022. **74**(1): p. 13-27.
9. Volkmann, E.R., et al., *Mycophenolate mofetil versus placebo for systemic sclerosis-related interstitial lung disease: an analysis of scleroderma lung studies I and II.* Arthritis Rheumatol, 2017. **69**(7): p. 1451-1460.
10. Kowal-Bielecka, O., et al., *Update of EULAR recommendations for the treatment of systemic sclerosis.* Ann Rheum Dis, 2017. **76**(8): p. 1327-1339.
11. Campochiaro, C. and Y. Allanore, *An update on targeted therapies in systemic sclerosis based on a systematic review from the last 3 years.* Arthritis Res Ther, 2021. **23**(1): p. 155.
12. Sandner, P. and J.P. Stasch, *Anti-fibrotic effects of soluble guanylate cyclase stimulators and activators: a review of the preclinical evidence.* Respir Med, 2017. **122**(Suppl 1): p. S1-S9.
13. Dees, C., et al., *Stimulators of soluble guanylate cyclase (sGC) inhibit experimental skin fibrosis of different aetiologies.* Ann Rheum Dis, 2015. **74**(8): p. 1621-1625.
14. Humbert, M., et al., *Riociguat for the treatment of pulmonary arterial hypertension associated with connective tissue disease: results from PATENT-1 and PATENT-2.* Ann Rheum Dis, 2017. **76**(2): p. 422-426.
15. Ghofrani, H.A., et al., *Riociguat for the treatment of pulmonary arterial hypertension.* N Engl J Med, 2013. **369**(4): p. 330–340.

16. Huntgeburth, M., et al., *Riociguat for the Treatment of Raynaud's Phenomenon: A Single-Dose, Double-Blind, Randomized, Placebo-Controlled Cross-Over Pilot Study (DIGIT).* Clin Drug Investig, 2018. **38**(11): p. 1061-1069.

17. Khanna, D., et al., *Riociguat in patients with early diffuse cutaneous systemic sclerosis (RISE-SSc): randomised, double-blind, placebo-controlled multicentre trial.* Ann Rheum Dis, 2020. **79**(5): p. 618-625.

18. van den Hoogen, F., et al., *2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative.* Ann Rheum Dis, 2013. **72**(11): p. 1747-1755.

19. Dobrota, R., et al., *Prediction of improvement in skin fibrosis in diffuse cutaneous systemic sclerosis: a EUSTAR analysis.* Annals of the Rheumatic Diseases, 2016. **75**(10): p. 1743-1748.

20. Khanna, D., et al., *Reliability and validity of the University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument.* Arthritis Rheum, 2009. **61**(9): p. 1257-63.

21. Ghofrani, H.A., et al., *Predictors of long-term outcomes in patients treated with riociguat for pulmonary arterial hypertension: data from the PATENT-2 open-label, randomised, long-term extension trial.* Lancet Respir Med, 2016. **4**: p. 361–371.

22. Simonneau, G., et al., *Predictors of long-term outcomes in patients treated with riociguat for chronic thromboembolic pulmonary hypertension: data from the CHEST-2 open-label, randomised, long-term extension trial.* Lancet Respir Med, 2016. **4**(5): p. 372-380.

23. Ghofrani, H.A., et al., *Riociguat for the treatment of chronic thromboembolic pulmonary hypertension.* N Engl J Med, 2013. **369**(4): p. 319-329.

24. Nathan, S.D., et al., *Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension (RISE-IIP): a randomised, placebo-controlled phase 2b study.* Lancet Respir Med, 2019. **7**(9): p. 780-790.

25. Nathan, S.D., et al., *Impact of lung morphology on clinical outcomes with riociguat in patients with pulmonary hypertension and idiopathic interstitial pneumonia: A post hoc subgroup analysis of the RISE-IIP study.* J Heart Lung Transplant, 2021. **40**(6): p. 494-503.

26. Bagnato, G., et al., *Autologous Haematopoietic Stem Cell Transplantation and Systemic Sclerosis: Focus on Interstitial Lung Disease.* Cells, 2022. **11**(5).

27. Hughes, M. and A.L. Herrick, *Digital ulcers in systemic sclerosis.* Rheumatology (Oxford), 2017. **56**(1): p. 14-25.

28. Nagaraja, V., et al., *A multicenter randomized, double-blind, placebo-controlled pilot study to assess the efficacy and safety of riociguat in systemic sclerosis-associated digital ulcers.* Arthritis Res Ther, 2019. **21**(1): p. 202.

29. Raghu, G., et al., *Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline.* Am J Respir Crit Care Med, 2018. **198**(5): p. e44-e68.

30. Nathan, S.D., et al., *HRCT evaluation of patients with interstitial lung disease: comparison of the 2018 and 2011 diagnostic guidelines.* Ther Adv Respir Dis, 2020. **14**: p. 1753466620968496.

Supplementary Appendix: Long-term extension results of RISE-SSc, a randomised trial of riociguat in patients with early diffuse cutaneous systemic sclerosis

Contents

Supplementary methods

Rescue therapy

From week 26 onwards, patients with the following had the opportunity to add rescue therapy to their randomised study medication. Rescue therapy was defined as treatment with an immunosuppressant drug, under the following situations:

- Worsening of skin disease (defined as >5 units and ≥25% increase in modified Rodnan skin score [mRSS]), or
- Relative decline in forced vital capacity (FVC) %predicted by ≥10%, or relative decline in FVC %predicted between ≥5% and <10% with associated relative decline in diffusing capacity of the lung for carbon monoxide %predicted by ≥15%, provided that the decline in FVC results in FVC <75% of predicted (confirmed by repeat pulmonary function testing within 1 month).

The decision to initiate rescue therapy was based on investigator discretion in eligible patients. Rescue therapy included any of the following four agents: methotrexate, mycophenolate mofetil, cyclophosphamide, or azathioprine.

Assessment of digital ulcer burden

Digital ulcers were defined as a full-thickness skin lesion with loss of epithelium, including lesions covered by eschar. Ulcers were to be >3 mm in maximal diameter. Healing was defined by re-epithelialisation with loss of pain and exudate. Pitting scars and hyperkeratotic lesions were always excluded. Digital ulcer net burden was assessed by the following methods:

- Ulcer count – ideally performed by the same healthcare professional at every visit:
    - Total ulcer counts
    - Distal counts: distal (fingertip) – any ulcer including skin area distal to proximal interphalangeal joint
- Ulcer burden:
    - Number of ulcers at time point minus baseline number of ulcers

- Visual analogue score for patient-reported severity of digital ulcers as part of the Scleroderma Health Assessment Questionnaire.

Safety follow-up assessment

The safety follow-up visit, 30 [+5] days after the last dose of study medication, evaluated:

- Height and weight
- Physical examination
- Oximetry
- Vital signs
- Blood sampling for safety
- Pregnancy test (if applicable)
- 12-lead electrocardiogram
- Adverse event (AE) recording
- Prior and concomitant therapy
- Survival status

Supplementary results

	Riociguat→riociguat (n=42)	**Placebo→riociguat (n=45)**
Age, years	52 (12)	49 (13)
Median (IQR)	51 (44–62)	50 (40–58)
Female, n (%)	31 (74)	34 (76)
Race, n (%)		
White	28 (67)	34 (76)
Black	0 (0)	1 (2)
Asian	11 (26)	10 (22)
Other or not reported	3 (7)	0 (0)

Disease duration, months	8·9 (7·8)*	8·9 (5·8)
Median (IQR)	7·2 (3·3–12·1)	8·7 (3·7–13·3)
mRSS	16·4 (3·2)	16·3 (4·2)
Median (IQR)	17·0 (14–19)	16·0 (12–21)
FVC %predicted	92 (21)	95 (17)
DL_{CO} %predicted (haemoglobin corrected)	78 (21)	78 (17)
Swollen joint count	2·0 (4·8)	0·9 (2·4)
Median (IQR)	0 (0–2)	0 (0–0)
Swollen joint count ≥1, n (%)	13 (31)	8 (18)
Tender joint count	3·5 (6·8)	1·5 (3·7)
Median (IQR)	0 (0–2)	0 (0–2)
Tender joint count ≥1, n (%)	20 (48)	14 (31)
Tendon friction rubs	2·3 (1·0)	4·1 (2·9)
Median (IQR)	2 (2–2)	3 (2–8)
Tendon friction rubs ≥1, n (%)	13 (31)	15 (33)
Digital ulcer count	0·1 (0·5)	0·1 (0·6)
Median (IQR)	0 (0–0)	0 (0–0)
Digital ulcer count ≥1, n (%)	4 (10)	2 (4)
Mean HAQ-DI, units	0·8 (0·6)	0·7 (0·7)
Median (range)	0·9 (0·0–2·0)	0·5 (0·0–2·4)
ILD by medical history, n (%)	11 (26)	11 (24)
Anti-RNA polymerase III positive, n (%)	9 (21)	11 (24)
Anti-Scl-70 (anti-topoisomerase I) positive, n (%)	17 (40)	16 (36)
Anti-centromere-B positive, n (%)	3 (7)	3 (7)

Supplementary Table 1: **Patient demographics and disease characteristics at the double-blind phase baseline (week 0) for patients who subsequently entered the open-label LTE**

Data are mean (SD), unless otherwise specified. DL_{CO}=diffusing capacity of the lung for carbon monoxide. FVC=forced vital capacity. HAQ-DI=Health Assessment Questionnaire-Disability Index. ILD=interstitial lung disease. IQR=interquartile range. LTE=long-term extension. mRSS=modified Rodnan skin score. RNA=ribonucleic acid. SD=standard deviation. *n=41.

Discontinuations due to AEs

Discontinuations in the riociguat→riociguat group were due to one case of malignant-stage tongue neoplasm and one case of skin ulcer. The latter was considered study drug related by the investigator.

Discontinuations in the placebo→riociguat group were due to one case each of abdominal distension, gastrointestinal angiodysplasia, intestinal obstruction, nausea, vomiting, diarrhoea, dysphagia, haematochezia, intestinal pseudo-obstruction, antineutrophil cytoplasmic antibody-positive vasculitis, systemic scleroderma, acute kidney injury, and skin hypertrophy. The AEs of abdominal distension, nausea, and vomiting were considered study drug related by the investigator.

AEs of special interest

Of the two patients in the riociguat→riociguat group who reported symptomatic hypotension, both reported mild hypotension that resolved during the study. In one patient, the event lasted 61 days, required a riociguat dose reduction, and was considered to be related to study treatment. In the other patient, the event lasted for 1 day, did not require riociguat dose adjustment, and was not considered to be related to study treatment.

Four patients in the placebo→riociguat group reported five events of symptomatic hypotension, all of which were considered to be related to study treatment. Three patients each had one episode of moderate hypotension that required riociguat dose reduction. Two episodes were not resolved during the study (duration unknown) and one episode resolved after 30 days. One patient had two episodes of mild hypotension, both of which lasted for 1 day, and recovered with no dose adjustment.

No serious events of haemoptysis were reported in the long-term extension. Non-serious haemoptysis (not considered to be an AE of special interest) was reported in one patient in each treatment group.

Adverse event	Riociguat→riociguat (n=42)	Placebo→riociguat (n=45)	Total (n=87)
Hypotension	3 (7)	7 (16)	10 (11)
Dizziness	3 (7)	4 (9)	7 (8)
Diarrhoea	1 (2)	4 (9)	5 (6)
Headache	1 (2)	4 (9)	5 (6)
Nausea	0	5 (11)	5 (6)
Peripheral oedema	1 (2)	3 (7)	4 (5)
Abdominal distension	0	3 (7)	3 (3)
Vomiting	0	3 (7)	3 (3)
Hyperhidrosis	2 (5)	0	2 (2)
Gastritis	1 (2)	1 (2)	2 (2)
Gastroenteritis	1 (2)	1 (2)	2 (2)
Palpitations	1 (2)	1 (2)	2 (2)
Amnesia	0	2 (4)	2 (2)
Anaemia	0	2 (4)	2 (2)
Arthralgia	0	2 (4)	2 (2)
Cough	0	2 (4)	2 (2)
Fatigue	0	2 (4)	2 (2)
Gastric ulcer	0	2 (4)	2 (2)
Gastro-oesophageal reflux disease	0	2 (4)	2 (2)

Supplementary Table 2: **Adverse events considered by the investigator to be related to riociguat treatment reported in >1 patient from week 52 to end of LTE**

Event, n (%)	Female			Male		
	Riociguat→riociguat (n=31)	Placebo→riociguat (n=34)	Total (n=65)	Riociguat→riociguat (n=11)	Placebo→riociguat (n=11)	Total (n=22)
AEs, n (%)	**30 (97)**	**31 (91)**	**61 (94)**	**11 (100)**	**11 (100)**	**22 (100)**
Study drug-related* AEs	25 (81)	21 (62)	46 (71)	8 (73)	9 (82)	17 (77)
Discontinuation of study drug due to AE	1 (3)	5 (15)	6 (9)	1 (9)	2 (18)	3 (14)
Maximum intensity for any AE, n (%)						
Mild	7 (23)	8 (24)	15 (23)	2 (18)	1 (9)	3 (14)
Moderate	16 (52)	15 (44)	31 (48)	5 (45)	7 (64)	12 (55)
Severe	7 (23)	8 (24)	15 (23)	4 (36)	3 (27)	7 (32)
Maximum intensity for study drug-related* AE, n (%)						
Mild	18 (58)	9 (26)	27 (42)	6 (55)	3 (27)	9 (41)
Moderate	6 (19)	8 (24)	14 (22)	2 (18)	5 (45)	7 (32)
Severe	1 (3)	4 (12)	5 (8)	0	1 (9)	1 (5)
SAE, n (%)	**7 (23)**	**13 (38)**	**20 (31)**	**5 (45)**	**4 (36)**	**9 (41)**
Study drug-related* SAEs	0	5 (15)	5 (8)	1 (9)	0	1 (5)
Discontinuation of study drug due to SAE	0	3 (9)	3 (5)	1 (9)	1 (9)	2 (9)

Supplementary Table 3: **Summary of AEs in male and female patients from week 52 to end of LTE**

Data are reported for AEs that started or worsened after first administration of study drug up to 2 days after end of treatment with study drug. AE=adverse event. LTE=long-term extension. SAE=serious AE. *Analyses of drug-related AEs were based on the assessment of causal relationship to study medication as determined by the investigator.

Event, n (%)	Riociguat→riociguat (n=42)		Placebo→riociguat (n=45)	
	No ILD at BL (n=31)	ILD at BL (n=11)	No ILD at BL (n=34)	ILD at BL (n=11)
Any AE	30 (97)	10 (91)	31 (91)	11 (100)
Nasopharyngitis	7 (23)	4 (36)	7 (21)	3 (27)
Gastro-oesophageal reflux disease	5 (16)	2 (18)	7 (21)	1 (9)
Skin ulcer	5 (16)	1 (9)	3 (9)	1 (9)
Arthralgia	4 (13)	0	5 (15)	1 (9)
Constipation	4 (13)	0	2 (6)	0
Diarrhoea	4 (13)	1 (9)	8 (24)	0
Pain in extremity	4 (13)	0	2 (6)	0
Vomiting	4 (13)	3 (27)	4 (12)	0
Bronchitis	3 (10)	2 (18)	0	0
Cough	3 (10)	3 (27)	3 (9)	0
Gastroenteritis	3 (10)	0	4 (12)	1 (9)

Headache	3 (10)	0	2 (6)	2 (18)
Hypotension	3 (10)	2 (18)	5 (15)	2 (18)
Upper respiratory tract infection	3 (10)	4 (36)	4 (12)	2 (18)
Contusion	2 (6)	0	1 (3)	2 (18)
Dizziness	2 (6)	1 (9)	5 (15)	1 (9)
Dyspnoea	1 (3)	2 (18)	1 (3)	2 (18)
Interstitial lung disease	2 (6)	3 (27)	2 (6)	3 (27)
Nausea	1 (3)	1 (9)	6 (18)	0
Influenza	1 (3)	2 (18)	2 (6)	2 (18)
Palpitations	1 (3)	2 (18)	1 (3)	0
Hypokalaemia	0	0	1 (3)	2 (18)

Supplementary Table 4: **Summary of AEs in patients with and without ILD from week 52 to end of LTE**

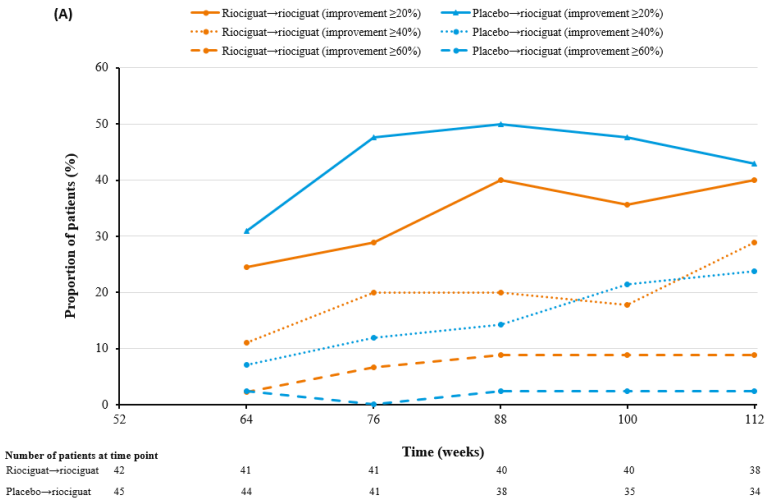
Table shows AEs reported in ≥10% of patients in any treatment group, where AEs started or worsened after first administration of study drug up to 2 days after end of treatment with study drug. AE=adverse event. BL=baseline. ILD=interstitial lung disease.

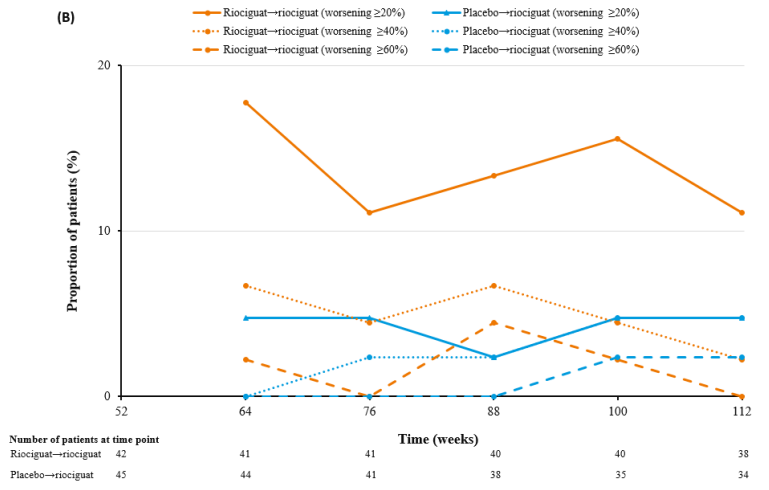
Event, n (%)	Riociguat→riociguat (n=42)		Placebo→riociguat (n=45)	
	No ILD at BL (n=31)	ILD at BL (n=11)	No ILD at BL (n=34)	ILD at BL (n=11)
Any respiratory AE	8 (26)	7 (64)	11 (32)	6 (55)
Acute respiratory distress syndrome	1 (3)	0	0	0
Alveolitis	0	0	1 (3)	0
Asthma	0	0	1 (3)	0
Cough	3 (10)	3 (27)	3 (9)	0
Dyspnoea	1 (3)	2 (18)	1 (3)	2 (18)
Epistaxis	2 (6)	1 (9)	0	1 (9)
Haemoptysis	0	1 (9)	0	1 (9)
Hypoxia	0	0	0	1 (9)
ILD	2 (6)	3 (27)	2 (6)	3 (27)
Nasal ulcer	0	0	0	1 (9)
Oropharyngeal pain	0	0	1 (3)	0
Productive cough	1 (3)	0	0	0
Pulmonary fibrosis	0	0	1 (3)	0

Pulmonary hypertension	0	0	0	1 (9)*
Pulmonary mass	1 (3)	0	0	0
Rales	0	0	2 (6)	0
Respiratory tract congestion	1 (3)	0	0	0
Sinus congestion	0	1 (9)	0	0
Upper respiratory tract inflammation	0	0	1 (3)	0

Supplementary Table 5: **Respiratory AEs in patients with and without ILD from week 52 to end of LTE**

Table shows respiratory, thoracic, and mediastinal disorders which started or worsened after first administration of study drug up to 2 days after end of treatment with study drug. AE=adverse event. BL=baseline. ILD=interstitial lung disease. LTE=long-term extension. *Assessed as mild.





Supplementary Figure 1: **Proportion of patients with (A) improvement (decrease) and (B) worsening (increase) in mRSS of ≥20, ≥40, and ≥60% from week 52 to week 112**

mRSS=modified Rodnan skin score.

Score (units)	Riociguat→riociguat				Placebo→riociguat			
	W0	W52	Change W0→52	Change W52→112	W0	W52	Change W0→52	Change W52→112
Long-term safety analysis set	**n=42**	**n=42**	**n=42**	**n=36**	**n=45**	**n=44**	**n=44**	**n=34**
FVC, %predicted	91·63 (20·67)	90·10 (19·07)	–1·54 (6·05)	–2·96 (6·18)	94·97 (16·99)	92·96 (15·23)	–2·47 (9·96)	–1·57 (6·85)
Median (range)	92·05 (45·00 to 123·50)	91·72 (44·00 to 121·0)	–1·40 (–18.00 to 11·00)	–4·05 (–21.1 to 12·00)	95·00 (65·40 to 144·0)	95·60 (48·1 to 133·5)	–1·00 (–35·00 to 17·00)	–2·40 (–17.00 to 16.00)
FVC (L)	3·11 (1·04)	3·02 (0·94)	–0·09 (0·20)	-0·11 (0·20)	3·30 (0·90)	3·22 (0·86)	–0·11 (0·32)	–0·08 (0·37)
Median (range)	2·94 (1·37 to 5·99)	2·88 (1·33 to 5·69)	–0·05 (–0·82 to 0·40)	–0·13 (–0·63 to 0·47)	3·15 (1·80 to 6.22)	3·05 (1·84 to 5·70)	–0·07 (–1·01 to 0·5)	–0·09 (–1·83 to 0·53)
DL_{CO} (mmol/min/kPa)	6·11 (2·30)	5·79 (1·92)	–0·32 (0·88)	–0·18 (0·66)	6·26 (1·94)	5·88 (1·84)*	–0·38 (0·90)*	–0·05 (0·92)
Median (range)	5·71 (3·52 to 17·21)	5·42 (3·30 to 13·70)	–0·33 (–3·51 to 1·81)	–0·08 (–1·84 to 1·75)	5·93 (3·13 to 12·49)	5·88 (2·67 to 11·75)	–0·30 (–3·52 to 1·14)	–0·25 (–2·65 to 2·01)
DL_{CO}, predicted (mmol/min/kPa)	7·89 (1·76)	7·77 (1·76)	–0·12 (0·23)	–0·07 (0·12)	8·21 (1·64)	8·20 (1·71)*	–0·01 (0·40)*	–0·08 (0·33)
Median (range)	7·66 (4·85 to 13·53)	7·40 (4·71 to 13·46)	–0·05 (–0·94 to 0·33)	–0·05 (–0·43 to 0·29)	8·27 (4·18 to 11·77)	8·24 (3·93 to 11·75)	–0.05 (–0·74 to 1·91)	–0·05 (–1·47 to 0·71)

ILD by medical history	n=11	n=11	n=11	n=10	n=11	n=10	n=10	n=9
FVC, %predicted	83·54 (24·05)	80·89 (23·59)	–2·66 (3·81)	–2·92 (4·04)	90·81 (23·97)	83·67 (21·65)	–8·72 (13·31)	–2·40 (8·06)
Median (range)	80·00 (45·00 to 123·5)	78·30 (44·00 to 119·5)	–2·00 (–8·00 to 4.50)	–4.05 (–7.00 to 5.00)	78·90 (65·40 to 144·0)	84·0 (48·1 to 114·5)	–5·65 (–35·0 to 5·00)	–2·80 (–17·00 to 11·20)
FVC (L)	2·71 (0·80)	2·62 (0·80)	–0·10 (0·11)	–0·14 (0·12)	2·95 (1.28)	2.78 (1.21)	–0.27 (0·35)†	–0·20 (0·66)
Median (range)	2·82 (1·37 to 3·96)	2·70 (1·33 to 3·81)	0·11 (–0·26 to 0·12)	–0.19 (–0.26 to –0.02)	2·59 (1·80 to 6·22)	2·33 (1·84 to 5·70)	–0·20 (–1·01 to 0·14)	–0.13 (–1.83 to 0.53)
DL_{CO} (mmol/min/kPa)	5·20 (1·75)	4·77 (1·36)	–0·43 (0·52)	–0·33 (0·74)	5·24 (1·78)	4·72 (1·57)†	–0·52 (0·84)	–0·47 (0·87)
Median (range)	5·04 (3·52 to 9·63)	4·45 (3·45 to 8·22)	–0·31 (–1·41 to 0·53)	–0.33 (–1.84 to 1.00)	4·91 (3·13 to 9·04)	4·26 (2·67 to 8·44)	–0·46 (–1·51 to 1·14)	–0.28 (–2.65 to 0.44)
DL_{CO}, predicted (mmol/min/kPa)	6·83 (1·02)	6·73 (1·06)	–0·10 (0·21)	–0·12 (0·16)	7·45 (1·61)	7·65 (1·98)	0·20 (0·70)	–0·16 (0·52)
Median (range)	7·10 (4·85 to 8·47)	7·06 (4·71 to 8.42)	–0·05 (–0·47 to 0·33)	–0.07 (–0.43 to 0.14)	7·37 (4·18 to 10·55)	7·15 (3·93 to 11·75)	–0·05 (–0·29 to 1·91)	–0.01 (–1.47 to 0.19)

Supplementary Table 6: **Changes in pulmonary function parameters from baseline to week 52 and week 52 to week 112 in the long-term safety analysis set and in patients with ILD by medical history**

All data are mean (SD). DL_{CO}=diffusing capacity of the lung for carbon monoxide. FVC=forced vital capacity. ILD=interstitial lung disease. SD=standard deviation. W=week.
*n=45; †n=11.

Score (units)	Riociguat→riociguat				Placebo→riociguat			
	W0 (n=16)	W52 (n=16)	Change W0→52 (n=16)	Change W52→112 (n=13)	W0 (n=15)	W52 (n=15)	Change W0→52 (n=15)	Change W52→112 (n=12)
Physical function	41·28 (5·69)	41·23 (6·92)	–0·06 (4·42)	–0·55 (7·37)	43·07 (7·38)	41·38 (7·97)	–1·69 (5·67)	1·23 (7·27)
Median (range)	41·10 (32·10 to 56·90)	39·75 (32·10 to 56·90)	0·00 (–7·40 to 11·60)	1·20 (–15·10 to 11·60)	43·40 (33·30 to 56·90)	43·40 (26·90 to 56·90)	0·00 (–8·90 to 8·90)	0·00 (–9·70 to 13·50)
Anxiety	49·45 (9·21)	48·56 (8·20)	–1·87 (9·18)*	0·47 (7·49)	52·19 (10·26)	51·21 (11·06)	–0·97 (5·02)	2·09 (6·63)
Median (range)	48·00 (40·30 to 65·30)	51·20 (40·30 to 63·40)	0·00 (–14·10 to 13·40)*	0·00 (–13·40 to 13·40)	53·70 (40·30 to 69·30)	53·70 (40·3 to 67·30)	0·00 (–10·90 to 9·70)	0·00 (–5·60 to 19·20)
Depression	48·43 (7·71)*	46·54 (7·41)	–2·50 (7·26)*	1·70 (4·61)	46·11 (8·68)	49·83 (9·12)	3·73 (6·97)	–3·25 (4·76)
Median (range)	49·00 (41·00 to 62.20)*	41·00 (41·00 to 63·90)	0·00 (–14·70 to 16·30)*	0·00 (–8·00 to 8·30)	41·00 (41·00 to 67·50)	51·80 (41·00 to 62·20)	0·00 (–5·30 to 21·20)	–1·40 (–14·70 to 0·00)
Fatigue	55·01 (10·23)*	53·71 (10·43)	–2·33 (7·63)*	3·03 (6·62)	52·63 (12·27)	54·52 (11·42)	1·89 (10·78)	–0·56 (8·29)
Median (range)	57·00 (39·70 to 69·00)	52·05 (39·70 to 75·80)	–1·9 (–13·9 to 13·1)	2·60 (–6·00 to 13·10)	55·10 (33·70 to 66·70)	51·00 (33·7 to 75·8)	0·00 (–18·10 to 24·80)	–0·95 (–12·30 to 13·60)

Sleep disturbance	51·52 (5·63)	52·34 (5·51)	0·83 (3·07)	–2·78 (4·99)	51·52 (4·62)	53·01 (5·49)	1·49 (5·34)	–1·28 (4·36)
Median (range)	51·45 (41·10 to 61·70)	53·35 (41·10 to 59·80)	0·90 (–5·10 to 6·70)	–2·10 (–12·30 to 3·80)	50·50 (46·20 to 63·80)	50·50 (46·20 to 61·70)	0·00 (–4·30 to 11·70)	0·0 (–11·7 to 5·90)
Social role satisfaction	42·56 (9·76)	45·99 (9·25)	3·43 (10·42)	–1·27 (7·77)	44·05 (12·75)	43·67 (8·99)	–0·38 (7·51)	0·42 (6·62)
Median (range)	42·55 (29·00 to 64·10)	44·80 (29·00 to 64·10)	0·00 (–8·40 to 35·10)	0·00 (–14·10 to 12·80)	44·8 (29·00 to 64·1)	38·80 (29·00 to 64·10)	0·00 (–12·80 to 9·80)	0·00 (–8·4. To 12·80)
Pain interference	57·29 (9·23)	58·73 (11·07)	1·44 (9·27)	0·08 (8·57)	55·70 (8·59)	54·55 (8·55)	–1·15 (7·04)	–0·23 (5·68)
Median (range)	58·40 (41·60 to 71·60)	59·15 (41·60 to 75·60)	0·00 (–14·00 to 25·00)	0·00 (–11·00 to 14·00)	55·60 (41·60 to 66·60)	55·60 (41·60 to 68·00)	–2·70 (–11·80 to 14·00)	0·00 (–10·40 to 10·40)

Supplementary Table 7: **Change in PROMIS-29 scores from baseline to week 52 and week 52 to week 112**

All data are mean (SD) unless stated otherwise. PROMIS-29=Patient-Reported Outcomes Measurement Information System. SD=standard deviation. W=week. ⁎n=15.

Score (units)	Riociguat→riociguat				Placebo→riociguat			
	W0 (n=42)	W52 (n=42)	Change W0→52 (n=42)	Change W52→112 (n=38)	W0 (n=45)	W52 (n=45)	Change W0→52 (n=45)	Change W52→112 (n=34)
Bodily pain	57·33 (27·57)	54·76 (27·75)	–2·57 (24·52)	0·13 (22·05)	57·96 (24·31)	64·11 (22·58)	6·16 (20·86)	–1·09 (23·29)
Median (range)	57·00 (12·00 to 100·0)	62·00 (10·00 to 100·0)	0·00 (–78·00 to 52·00)	0·00 (–43·00 to 53·00)	62·0 (10·00 to 100·0)	62·00 (10·00 to 100·0)	9·00 (–39·00 to 59·00)	0·00 (–59·00 to 38·00)
General health	47·38 (21·44)	45·67 (20·75)	–1·71 (18·05)	–1·58 (10·04)	54·71 (21·16)	50·82 (19·95)	–3·89 (18·23)	3·68 (12·42)
Median (range)	45·00 (12·00 to 97·00)	46·00 (10·00 to 97·00)	–3.50 (–45·00 to 50·00)	0·00 (–27·00 to 22·00)	52·00 (5·00 to 100·0)	52·00 (5·00 to 87·00)	–5·00 (–45·00 to 47·00)	2·50 (–22·00 to 40·00)
Mental health	68·21 (20·71)	71·43 (18·88)	3·21 (17·63)	0·26 (11·74)	69·11 (19·26)	68·89 (18·21)	–0·22 (18·06)	3·09 (14·04)
Median (range)	70·00 (15·00 to 100·0)	75·00 (35·00 to 100·0)	0·00 (–30·00 to 40·00)	0·00 (–30·00 to 25·00)	75·00 (20·00 to 100·0)	75·00 (30·00 to 100·00)	0·00 (–40·00 to 50·00)	2·50 (–35·00 to 30·00)
Physical functioning	63·57 (24·53)	64·29 (24·85)	0·71 (15·52)	–1·97 (10·10)	67·00 (26·23)	69·59 (25·73)	2·59 (17·97)	–0·97 (16·33)
Median (range)	65·01 (15·00 to 100·0)	65·01 (15·00 to 100·0)	0·00 (–35·01 to 30·00)	0·00 (–24·99 to 15·00)	75·00 (0·00 to 100·0)	75·00 (10·00 to 100·0)	0·00 (–29·99 to 50·00)	0·00 (–45·00 to 29·99)
Role emotional	76·59 (29·00)	75·79 (28·97)	–0·79 (30·01)	–3·07 (24·23)	75·18 (25·03)	75·74 (25·05)	0·56 (25·52)	2·45 (18·64)

Median (range)	87·50 (8·33 to 100·0)	87·50 (0·00 to 100·0)	0·00 (–75·00 to 75·00)	0·00 (–66.67 to 50·00)	75·00 (8·33 to 100·0)	75·00 (16·67 to 100·0)	0·00 (–58·33 to 66·67)	0·00 (–33·33 to 50·00)
Role physical	64·88 (29·15)	58·93 (30·25)	–5·95 (23·95)	–0·16 (20·21)	66·39 (28·46)	65·14 (29·48)	–1·25 (22·56)	6·43 (21·95)
Median (range)	65·63 (6·25 to 100·0)	56·25 (0·00 to 100·0)	0·00 (–75·00 to 37·50)	0·00 (–62.50 to 50·00)	68·75 (12·50 to 100·0)	75·00 (6·25 to 100·0)	0·00 (–68·75 to 50·0)	0·00 (–75·00 to 62·50)
Social functioning	71·43 (25·94)	74·11 (26·96)	2·68 (23·84)	–0·99 (27·17)	71·67 (25·34)	74·44 (26·11)	2·78 (24·70)	1·10 (24·69)
Median (range)	75·00 (12·50 to 100·0)	81·25 (25·00 to 100·0)	0·00 (–50·00 to 50·00)	0·00 (–75·00 to 37·50)	75·00 (25·00 to 100·0)	75·00 (12·50 to 100·0)	0·00 (–50·00 to 75·00)	0·00 (–75·00 to 50·00)
Vitality	50·45 (19·83)	51·79 (20·3)	1·34 (14·11)	–4·77 (13·43)	52·36 (22·82)	53·47 (23·75)	1·11 (18·43)	–1·65 (14·21)
Median (range)	50·00 (12·50 to 87·50)	53·13 (6·25 to 87·50)	0·00 (–31·25 to 31·25)	–3·13 (–50·00 to 18·75)	50·00 (0·00 to 100·0)	56·25 (0·00 to 87·50)	0·00 (–50·00 to 37·50)	0·00 (–31·25 to 31·25)
Mental component score	48·07 (11·29)	49·50 (10·49)	1·43 (10·46)	–0·94 (8·18)	47·84 (10·42)	47·92 (10·22)	0·08 (10·44)	0·98 (6·34)
Median (range)	49·51 (25·68 to 64·38)	51·01 (25·40 to 65·76)	1·14 (–17·51 to 25·14)	–1·12 (–22·96 to 14·82)	49·83 (17·56 to 65·92)	49·72 (22·36 to 61·84)	–1.15 (–18·89 to 27·91)	0·63 (–13·82 to 13·92)
Physical component score	42·81 (9·66)	41·35 (10·22)	–1·46 (6·10)	–0·36 (5·09)	44·55 (9·68)	45·12 (8·48)	0·58 (6·24)	0·37 (6·73)

Median (range)	41·73 (22·92 to 65·96)	40·92 (22·58 to 59·18)	–1·58 (–14·79 to 12·58)	–0·22 (–10·28 to 11·33)	44·33 (24·63 to 61·90)	45·97 (25·69 to 58·24)	–0·76 (–10·77 to 14·71)	0·96 (–20·84 to 10·72)
Mental health enhanced score	9·33 (7·25)	8·14 (6·30)	–1·19 (5·96)	0·01 (4·22)	8·96 (6·65)	8·94 (6·18)	–0·02 (6·39)	–0·88 (5·03)
Median (range)	8·35 (0·00 to 31·12)	6·74 (0·00 to 21·02)	0·00 (–13·24 to 9·76)	0·00 (–8·97 to 11·05)	6·74 (0·00 to 28·25)	6·74 (0·00 to 23·25)	0·00 (–17·54 to 14·90)	–0.67 (–9.76 to 14·90)
Health utility index	0·66 (0·12)	0·67 (0·12)	0·00 (0·10)	–0·01 (0·08)*	0·67 (0·12)	0·68 (0·12)†	0·01 (0·10)	0·01 (0·09)
Median (range)	0·64 (0·42 to 0·93)	0·64 (0·49 to 0·93)	–0.01 (–0·17 to 0·29)	0·01 (–0.20 to 0·17)	0·66 (0·49 to 1·00)	0·64 (0·46 to 0·93)	0·00 (–0·28 to 0·21)	0·01 (–0·23 to 0·22)

Supplementary Table 8: **Change in SF-36 scores from baseline to week 52 and week 52 to week 112**

All data are mean (SD) unless stated otherwise. SD=standard deviation. SF-36=Short Form 36. W=week. *n=36; †n=44.

Score (units)	Riociguat→riociguat				Placebo→riociguat			
	W0 (n=42)	W52 (n=42)	Change W0→52 (n=42)	Change W52→112 (n=38)	W0 (n=45)	W52 (n=45)	Change W0→52 (n=45)	Change W52→112 (n=34)
Pain in past week	0·92 (0·90)	0·91 (0·84)	–0·02 (0·75)	–0·14 (0·68)	0·80 (0·78)	0·78 (0·76)	–0·02 (0·69)	–0·20 (0·66)
Median (range)	0·69 (0·00 to 3·00)	0·56 (0·00 to 2·70)	0·00 (–2·10 to 1·98)	0·00 (–1·92 to 1·89)	0·42 (0·00 to 2·70)	0·60 (0·00 to 2·70)	0·00 (–1·68 to 1·17)	–0·05 (–2·2 to 1·05)
Intestinal problems in past week	0·57 (0·81)*	0·65 (0·85)	0·09 (0·63)*	0·01 (0·76)	0·34 (0·59)	0·44 (0·71)	0·10 (0·68)	–0·05 (0·61)
Median (range)	0·06 (0·00 to 2·58)*	0·20 (0·00 to 2·88)	0·00 (–1·80 to 1·95)*	0·00 (–1·59 to 2·61)	0·03 (0·00 to 2·19)	0·03 (0·00 to 2·37)	0·00 (–1·26 to 1·86)	0·00 (–1·83 to 1·17)
Breathing problems in past week	0·50 (0·76)	0·52 (0·79)	0·02 (0·38)	–0·01 (0·54)	0·30 (0·54)	0·45 (0·68)	0·16 (0·52)	–0·08 (0·43)
Median (range)	0·06 (0·00 to 2·67)	0·14 (0·00 to 2·82)	0·00 (–1·29 to 0·75)	0·00 (–1.62 to 1·20)	0·06 (0·00 to 2·25)	0·09 (0·00 to 2·40)	0·00 (–0·75 to 1·65)	0·00 (–1·95 to 0·78)
Raynaud's in past week	0·68 (0·83)*	0·62 (0·79)	–0·06 (0·74)*	0·16 (0·67)	0·63 (0·79)	0·55 (0·71)	–0·08 (0·68)	–0·11 (0·51)
Median (range)	0·24 (0·00 to 2·40)*	0·21 (0·00 to 2·64)	–0·06 (–1·83 to 2·37)*	0·00 (–1·23 to 2·04)	0·15 (0·00 to 2·67)	0·24 (0·00 to 2·28)	0·00 (–1·98 to 1·02)	0·00 (–1·86 to 1·02)

Finger ulcers in past week	0·25 (0·55)	0·27 (0·59)	0·02 (0·68)	–0·02 (0·57)	0·26 (0·60)	0·35 (0·70)	0·09 (0·77)	–0·05 (0·50)
Median (range)	0·00 (0·00 to 2·10)	0·00 (0·00 to 2·55)	0·00 (–2·10 to 2·10)	0·00 (–1·35 to 2·85)	0·00 (0·00 to 2·28)	0·00 (0·00 to 2·70)	0·00 (–2·19 to 2·37)	0·00 (–2·04 to 1·05)
Overall disease rating	0·86 (0·76)	1·01 (0·87)	0·15 (0·75)	–0·02 (0·61)	1·05 (0·85)	0·87 (0·81)	–0·18 (0·84)	–0·13 (0·59)
Median (range)	0·63 (0·00 to 3·00)	0·74 (0·00 to 3·00)	0·00 (–1·32 to 2·49)	–0·02 (–1·38 to 1·56)	0·99 (0·00 to 3·00)	0·57 (0·00 to 2·88)	–0·03 (–2·88 to 1·56)	–0·11 (–1·83 to 1·47)

Supplementary Table 9: **Change in S-HAQ scores from baseline to week 52 and week 52 to week 112**

All data are mean (SD) unless stated otherwise. SD=standard deviation. S-HAQ=Scleroderma Health Assessment Questionnaire. W=week. *n=41.

	Riociguat→riociguat (n=42)	Placebo→riociguat (n=45)
Any	32 (76)	32 (71)
Corticosteroids	23 (55)	17 (38)
Calcium channel blockers	12 (29)	8 (18)
Biological DMARDs	3 (7)	0
Non-biological DMARDs	12 (29)	14 (31)
NSAIDs	20 (48)	19 (42)
Glyceryl trinitrate	2 (5)	0
Pentoxifylline	0	1 (2)
PDE5is	3 (7)	2 (4)
Prostacyclins	3 (7)	3 (7)

Supplementary Table 10: **Concomitant medication from week 52 to the end of the study**

Data are n (%). DMARD=disease-modifying antirheumatic drug. NSAID=non-steroidal anti-inflammatory drug. PDE5i=phosphodiesterase type 5 inhibitor.