RISE-SSc: Riociguat in diffuse cutaneous systemic sclerosis

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Abstract

RISE-SSc is a randomized, double-blind, placebo-controlled phase 2 study investigating the efficacy and safety of riociguat in patients with diffuse cutaneous systemic sclerosis (dcSSc). Based on positive results from riociguat trials in patients with pulmonary hypertension and chronic thromboembolic pulmonary hypertension in combination with the known antiproliferative and antifibrotic effects seen in animal models, patients with SSc may benefit from treatment with riociguat. Patients with SSc meeting the ACR/EULAR systemic sclerosis classification criteria with diffuse cutaneous SSc (dcSSc) subset per LeRoy criteria, and a disease duration of less than or equal to 18 months will be randomized to placebo or riociguat 0.5 mg (up-titrated to a maximum dose of 2.5 mg TID over 10 weeks) and maintained on therapy for a total of 52 weeks. During the first 10 weeks of the long-term extension phase, placebo subjects will be up-titrated on riociguat, and all patients will be followed for up to 6 years. The primary endpoint of change in modified Rodnan skin score (mRSS) from baseline will be assessed at 52 weeks, as will be secondary endpoints such as mRSS progression and regression rates, patient quality of life, digital ulcer burden, and change in forced vital capacity and carbon monoxide diffusing capacity. This review will further define the clinical rationale for the use of riociguat in the treatment of SSc and provide details on study protocol, design, and outcome reporting.

Trial registration

Clinicaltrials.gov identifier: NCT02283762.

1. Background and rationale

Riociguat is a soluble guanylate cyclase (sGC) modulator being investigated in a subset of scleroderma known as diffuse cutaneous systemic sclerosis (dcSSc) [1], which can be a severely incapacitating and life-threatening rheumatic disease [2]. Patients with early dcSSc (less than 5 years) are at risk for visceral complications in the heart, lungs, kidneys, and gastrointestinal tract [3].

The extent of skin involvement in SSc is measured clinically using the modified Rodnan skin score (mRSS); skin fibrosis in dcSSc involves the fingers, hands, and forearms, extends proximal to the elbows and/or knees, and may also involve the face, anterior chest, and abdomen [3]. In patients with dcSSc, skin changes are usually preceded by a brief duration of Raynaud's phenomenon (RP) [4]. Patients with untreated concomitant dcSSc and pulmonary hypertension (PH) have a median survival of approximately 18 months from time of diagnosis [5], [6].

Treatment of SSc is usually organ specific, and there are no therapies that result in major skin improvement for most patients [7]. However, calcium channel blockers are widely used in the treatment of RP [8], and phosphodiesterase-5 (PDE5) inhibitors (eg, sildenafil) have vasodilatory properties that may improve RP and reduce digital ischemia and ulceration in SSc [9]. Available treatment options only target disease symptoms, and there is currently no disease-modifying drug to reverse the vascular and fibrotic damage from dcSSc [7].

In patients with early dcSSc, a randomized, placebo-controlled trial of methotrexate (a folic acid analog) found weak evidence and borderline statistical effect for its use in SSc; additional trials with drugs such as recombinant human relaxin (a polypeptide hormone) and d-penicillamine have shown negative results [10], [11], [12]. Additional drugs which may have antifibrotic effects (ie, tyrosine kinase inhibitors, cyclophosphamide) have not yet been investigated in large, randomized trials [13], [14].

Recent preclinical studies of BAY 41-2272, an sGC stimulator, demonstrated promising antifibrotic findings in mice with bleomycin-induced dermal fibrosis and tight-skin (Tsk-1) mice overexpressing transforming growth factor (TGF)β [15], [16]. BAY 42-2272 inhibited TGF-β1–induced fibroblast activation and collagen release and, in bleomycin models, halted the development of fibrosis, prevented dermal and hypodermal thickening, and reduced the number of dermal fibroblasts. A murine model of dermal fibrosis demonstrated a 52% decrease in skin thickening, a 59% decrease in hydroxyproline content, and a 60% decrease in the myofibroblast count following treatment with BAY 41-2272 [16]. Given the safety and efficacy of approved sGC stimulators such as riociguat, there may be the potential for simultaneous treatment of vascular disease and fibrosis in SSc [15], [16]. A phase II study of riociguat in patients with pulmonary arterial hypertension (PAH) found that patients with SSc-related PAH also benefited from therapy [17]. A recent preclinical trial by Dees et al. compared the antifibrotic effects of riociguat and sildeafil in the Tsk-1 model, in bleomycin-induced fibrosis, and in sclerodermatous chronic graft-versus-host disease (cGvHD) [18]. Riociguat reduced skin thickening, collagen accumulation, and myofibroblast differentiation in a dose-dependent manner in the Tsk-1 and bleomycin models, and reduced GI tract fibrosis in the cGVHD model. Sildenafil showed mild antifibrotic effects which were significantly less pronounced than those of riociguat [18]. Riociguat is approved for the treatment of PAH based on its efficacy in patients with idiopathic PAH and connective tissue disorders in the PATENT studies [19], and a phase II study of riociguat in patients with SSc is currently recruiting. For treatment of patients with SSc, it is anticipated that riociguat may ameliorate fibrotic disease by acting through pathways mediated by TGFβ [15]. There is a large unmet need in treatment of dcSSc, and a reason for publishing this full

protocol is to provide awareness of a large trial in early dcSSc. This multicenter study will have a long-term, open-label extension and will collect data from many domains important in SSc.

2. Methods

In this multinational randomized (1:1), double-blind, placebo-controlled, parallel-group study, approximately 200 patients are planned for enrollment to randomize 130 patients between study arms (approximately 65 patients to the riociguat group and 65 to the placebo group) (NCT02283762; https://clinicaltrials.gov/ct2/show/NCT02283762). The overall objectives of this study are to evaluate the efficacy and safety of 52 weeks of treatment with riociguat versus placebo in patients with dcSSc. The study design consists of a placebo-controlled treatment phase followed by a long-term extension, as follows: a screening phase of up to 2 weeks followed by a 52-week double-blind main treatment phase where patients will be dose titrated over a 10-week period and maintained on therapy for up to 42 weeks; the open-label long-term extension phase will dose-titrate patients formerly on placebo onto riociguat over a 10-week period and then maintain them on therapy for up to 42 weeks; the long-term extension phase will continue up to 6 years after the trial is completed.

2.1. Inclusion criteria

Men and women aged 18 years and older will be included in the study. In addition, at the screening visit study subjects must have SSc, as defined by the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2013 criteria [14]; dcSSc according to the LeRoy criteria [1]; disease duration of ≤18 months (defined as time from the first non-Raynaud's phenomenon manifestation); skin involvement as per the mRSS (≥10 and ≤22 units); forced vital capacity (FVC) ≥45% of predicted; and diffusion capacity of the lung for carbon monoxide (DLCO) ≥40% of predicted (hemoglobin-corrected). The rationale to take a baseline mRSS between 10 and 22 as an inclusion criterion is based on analysis from the EUSTAR database showing increased likelihood of progressive skin fibrosis within this range [20].

Woman of childbearing potential must have a negative serum pregnancy test and agree to use adequate contraception. "Adequate contraception" is defined as any combination of at least 2 effective methods of birth control, of which at least one is a physical barrier. This applies from the signing of consent until 30 (+5) days after the last study drug administration.

2.2. Exclusion criteria

Subjects will be excluded if, at screening, they have limited cutaneous SSc, had major surgery (including joint surgery) within 8 weeks prior to screening, hepatic insufficiency classified as Child-Pugh C, estimated glomerular filtration rate (eGFR) <15mL/min/m2 (Modification of Diet in Renal Disease formula) or on dialysis, any prior history of renal crisis, systolic blood pressure (SBP) <95 mmHg sitting, resting heart rate <50 beats per minute (BPM), left ventricular ejection fraction <40% prior to screening, diagnosed PAH as determined by right heart catheterization, pulmonary disease with FVC <45% of predicted or DLCO (hemoglobin-corrected) <40% of predicted, and current hemoptysis or pulmonary hemorrhage. Excluded and permitted prior and concomitant medications are listed in Table 1.

Table 1. Excluded and permitted prior and concomitant therapies.

Excluded prior and concomitant therapy	Permitted prior and concomitant therapy
Concomitant use of nitric oxide (NO) donor drugs, PDE inhibitors, and prostacyclin analogs	Oral corticosteroids (≤10 mg/day of prednisone or equivalent)
Treatment with methotrexate, cyclophosphamide, hydroxychloroquine, cyclosporine A, azathioprine, mycophenolate mofetil, rapamycin, colchicine, d-penicillamine, or IV immunoglobulin within 4 weeks prior to screening	Nonsteroidal anti-inflammatory drugs
Treatment with etanercept within 2 weeks	Angiotensin converting enzyme inhibitors
Treatment with infliximab, leflunomide, certolizumab, golimumab, adalimumab, abatercept, or tocilizumab within 8 weeks	Calcium channel blockers if stable for ≥2 weeks before treatment, including at baselinea
Anakinra within 1 week; no history of bone marrow transplant or lymphoid irradiation	
Treatment with rituximab or anti-CD20 antibodies within 6 months	

These treatments will also be allowed as new-onset during the study at the discretion of the investigator to treat SSc-specific adverse events (eg, Raynaud's phenomena, joint inflammation, new onset renal crisis).

2.3. Efficacy variables

The primary efficacy outcome measure will be change in mRSS from baseline to Week 52.

Secondary efficacy measures include mRSS progression rate (defined as increase in mRSS by >5 units and >25% from baseline) and mRSS regression rate (defined as decrease in mRSS by >5 units and >25% from baseline); patient's and physician's global assessment; HRQoL using Medical Outcomes Study 36-item Short Form (SF-36) and the Scleroderma Health Assessment Questionnaire (SHAQ) (consisting of the HAQ Disability Index and 6 visual analog scales) [21]; digital ulcer count at each and overall ulcer burden (defined as total number of ulcers at a defined time point minus number of ulcers at baseline) and proportion of patients who do not develop new ulcers; change in FVC % predicted and DLCO % predicted; Combined Response Index for Systemic Sclerosis (CRISS); and need for escape therapy.

2.4. Safety

Any adverse event [AE] and any serious AE (SAE) that results in death, is life-threatening, or requires inpatient hospitalization or prolongation of existing hospitalization will be collected and reported. The intensity of each AE/SAE will be classified as mild, moderate, or severe. The investigator is obliged to report AE/SAEs. All non-serious events will be assessed and recorded during the specified observational phase (from signing the informed consent form up to the follow-up visit 30 [+5] days after last study medication intake), whether believed to be related or unrelated to the treatment. As

per good clinical practice and in line with regulatory authorities, all SAEs will be collected and reported to the sponsor within 24 h from the time of awareness.

2.5. Statistical analysis

All variables will be analyzed descriptively with appropriate statistical methods. If not mentioned otherwise, all statistical tests will be performed with a type I 2-sided error rate of α = 5%; statistical analyses will be performed using SASF or the primary outcome (mRSS), assuming a standard deviation (SD) of 8 units, a power of 80% and a 2-sided significance level of 5%, with a 1:1 randomization, then to detect a placebo-adjusted difference of 4 units, 128 patients would be required to be valid for the intent-to-treat analysis. Allowing for up to two patients randomized and not treated, 130 randomized patients are planned.

In the efficacy analyses, countries will be clustered by geographic region. The decision on country pooling (which countries belong to a particular region) will be made before unblinding. Statistical analyses will be adjusted by countries and regions only if there are sample sizes of at least 20 patients in a minimum of two subgroups. Otherwise, the sample sizes will be too small for a test of regional differences.

Due to the large amount of data that will be prospectively collected and scrutinized, there may be other exploratory analyses performed that could enable understanding of SSc clinical trial endpoints and/or effects that are observed in the study.

3. Discussion

Riociguat has both vasoactive and antifibrotic effects, and the clinical trial described will examine efficacy and safety of riociguat as a novel therapeutic drug in patients with early dcSSc, where there is unmet medical need. There is a rationale for riociguat demonstrating anti-fibrotic effects. Compared with PDE5 inhibitors, an animal study with sildenafil alone, riociguat alone, or a combination of sildenafil and riociguat found riociguat alone or in combination attenuated pulmonary fibrosis better than sildenafil alone [22].

Most dcSSc trials have used change in mRSS after 6 or 12 months as the primary endpoint. The sample size for this study was based on four published articles [11], [23], [24], [25] that estimated the standard deviation with an upper estimate of 8.0 units of the mRSS. In order to design this study appropriately in terms of its inclusion criteria, an observational study which was a subset of patients enrolled in the EULAR Scleroderma Trials and Research (EUSTAR) group was performed to consider predictive parameters it identified for the progression of skin fibrosis within 1 year in patients with dcSSc [26]. The evidence-based criteria identified and validated in EUSTAR for the prediction of worsening skin fibrosis include joint synovitis, short disease duration (<15 months), low mRSS at baseline, and interaction between female gender and short disease duration [26].

4. Conclusions

This RCT should yield valuable data with respect to a potential role of riociguat in SSc beyond its proven benefit in patients with PAH. Furthermore, in vitro experiments and animal models have confirmed the antifibrotic effects of riociguat, and the predictive value of EUSTAR criteria will help to identify patients for participation in the trial.

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