An Investigator Initiated, Double-Blind, Proof-of-Concept, Randomized Placebo-Controlled Trial of Riociguat in Systemic Sclerosis-associated Digital Ulcers

SCLERODERMA PROGRAM
INTERNAL MEDICINE
RHEUMATOLOGY
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INTRODUCTION

- Digital ulcers (DUs) are seen in approximately 30% of the patients with systemic sclerosis (SSc) and cause substantial morbidity. (1,2).
- The soluble guanylate cyclase stimulator riociguat (RIO) is a vasodilator and has efficacy in patients with pulmonary arterial hypertension associated with connective tissue disease.

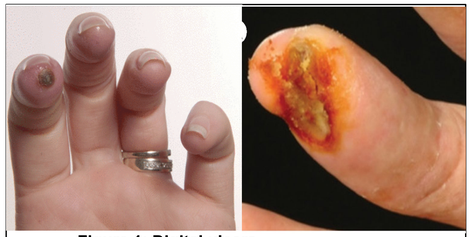


Figure 1: Digital ulcers

OBJECTIVE

We present results from an investigator-initiated, multicenter double-blind, proof-of-concept, randomized placebo-controlled trial (NCT02915835), which evaluated the efficacy and safety of RIO in patients with systemic sclerosis-associated digital ulcers (SSc-DU).

METHODS

- Eligible participants: SSc patients with at least one visible, active ischemic DU or painful indeterminate DU at screening, located at or distal to the proximal interphalangeal joint, and that developed or worsened within 8 weeks prior to screening.
- Participants were randomized 1:1 to placebo (PBO) or RIO in individualized doses during an 8-week titration period, followed by an 8-week stable dosing period (Figure 2). This was followed by an optional 16-week open-label extension phase in eligible participants
- The primary endpoint was the change from baseline to week 16 in net ulcer burden (NUB), analyzed using ANCOVA. Other endpoints included plasma biomarkers and treatment-emergent adverse events (AEs).

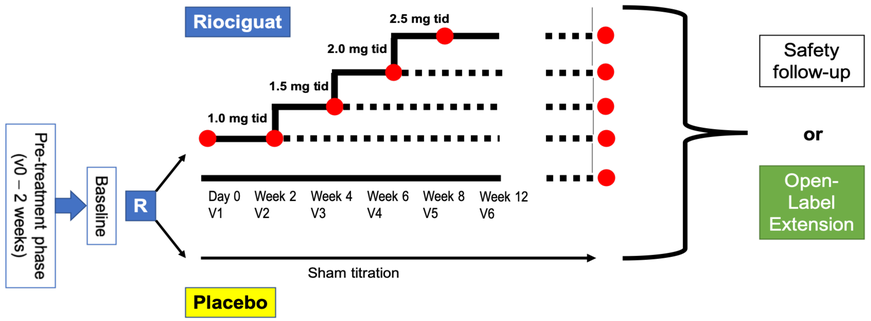


Figure 2: Study design

RESULTS

Table 1: Baseline characteristics of all of the randomized patients

Characteristics		Double-blind phase		
		PBO (n=8)	RIO (n=9)	All patients (n=17)
Age in years, mean (SD)		61 (17)	43 (14)	51 (18)
Female, n (%)		5 (63)	8 (89)	13 (76)
Race, Caucasian, n (%)		7 (88)	6 (67)	13 (76)
SSc subset, n (%)	Limited cutaneous SSc	4 (50)	5 (56)	9 (53)
	Diffuse cutaneous SSc	4 (50)	4 (44)	8 (47)
Time in years, mean (SD)	Since SSc diagnosis	15 (8.2)	6.2 (5.8)	10.4 (8.2)
	Since first non-RP symptom	17.5 (11.2)	7.1 (6.0)	12 (10.1)
	Since first RP symptom	14.5 (7.9)	7.5 (6.6)	11 (7.9)
DU, mean (SD)	Total number	2.5 (1.7)	2.7 (1.8)	2.6 (1.7)
	Active DU	1.4 (1.1)	1.1 (1.0)	1.2 (1.0)
	Indeterminate DU	1.1 (1.4)	1.6 (1.3)	1.3 (1.3)
	Net Ulcer Burden	2.5 (2.0)	2.4 (1.4)	2.5 (1.7)
Raynaud's attacks, mean (SD)	Raynaud's Condition Score	3.4 (2.2)	5.4 (1.6)	4.5 (2.1)
	Number of attacks per day	2.2 (1.7)	4.3 (1.7)	3.3 (2.0)
Autoantibodies, n (%)	Anti-centromere B	3 (38)	3 (33)	6 (35)
	Anti–topoisomerase I	3 (38)	2 (22)	5 (29)
Baseline use of vasodilators, n (%)		1 (13)	1 (11)	2 (12)

SD = standard deviation, PBO = Placebo, RIO = riociguat, SSc= systemic sclerosis, DU = digital ulcers

Table 2: Changes from baseline to week 16 in primary and secondary efficacy end points

Characteristics (LS mean)	PBO (N=8)	RIO (N=7)	Treatment Difference (95% CI)	p-value
Net Ulcer Burden	-0.98	-1.22	-0.24 (-1.46 to 0.99)	0.706
Patient global assessment	-1.19	0.31	1.50 (-1.30 to 4.30)	0.27
Patient assessment - severity of RP	-1.41	-3.47	-2.06 (-4.63 to 0.51)	0.11
Patient assessment - severity of DU	-4.00	-4.63	-0.63 (-3.68 to 2.41)	0.66
Pain during RP attack (0-100)	-7.01	-0.30	6.71 (-14.01 to 27.43)	0.49
Numbness during RP attack (0-100)	-15.44	-19.73	-4.28 (-33.44 to 24.87)	0.75
Tingling during RP attack (0-100)	-7.49	1.18	8.67 (-13.75 to 31.09)	0.41
Raynaud's condition score	-0.82	-1.15	-0.33 (-2.60 to 1.94)	0.76
Number of Raynaud's attacks per day	-0.96	-1.24	-0.28 (-1.36 to 0.79)	0.57
Duration of Raynaud's attacks (min)	150.3	-44.8	-195.1 (-683.7 to 293.5)	0.40
Physician global assessment	-0.66	-1.17	-0.51 (-2.27 to 1.25)	0.54
Physician assessment - severity of RP	-1.86	-3.00	-1.15 (-3.51 to 1.22)	0.32
Physician assessment - severity of DU	-3.81	-3.54	0.27 (-2.55 to 3.10)	0.84
SHAQ-DI overall disease (0-150)	-35.74	-50.35	-14.60 (-45.48 to 16.27)	0.32
HAQ-DI	-0.06	-0.01	0.04 (-0.44 to 0.53)	0.84

LS mean=least squares mean (ANCOVA model), with treatment and baseline value as co-variates; DU = digital ulcer, RP = Raynaud's phenomenon, SHAQ DI = Scleroderma Health Assessment Questionnaire Disability Index, VAS = visual analogue scale, GI = gastrointestinal, PROMIS = Patient Reported Outcomes Measures Information System, HAQ DI = Health Assessment Questionnaire Disability Index, HDISS DU = Hand Disability in SSc DU

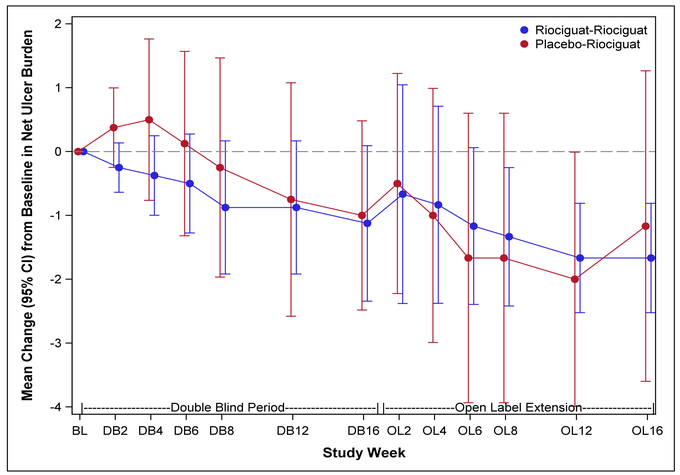
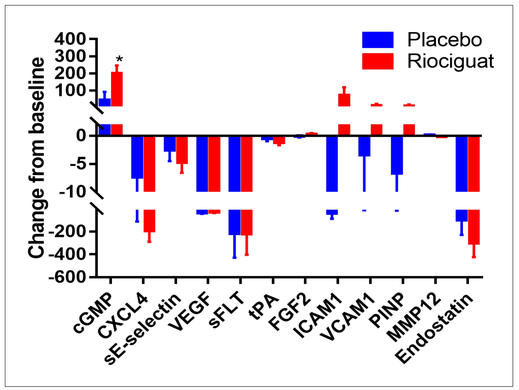


Figure 3: Mean trend over time – change in net ulcer burden

DU net burden : The total number of active and indeterminate digital ulcers at an assessment.



Open label extension

- Participants in the RIO-RIO arm had complete healing of their DUs.
- Improvement in NUB in both PBO-RIO and RIO-RIO arms

Safety and tolerability

- Four participants experienced 5 serious AE (4 in RIO and 1 in PBO); none was considered related to study medication.

Figure 4: Plasma biomarker changes from baseline to week 16

*p<0.05; Data represented as mean

CONCLUSION

- In patients with SSc-DU, treatment with RIO did not reduce the number of NUB compared with PBO over 16-weeks. With longer duration of treatment completing healing ulcers was noted.
- The safety profile of RIO was similar to that previously reported.
- The vascular markers (cGMP) may reflect biological activity of RIO.
- The negative results may reflect small number of patients, low number of NUB at baseline, moderate-to-severe vasculopathy with long term disease, and difficulty to recruit patients in the era of widespread use of PDE5 inhibitors.

REFERENCES

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