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.

**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).
- 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).

**RESULTS**

- **Characteristics**
  - **Table 1: Baseline characteristics of all of the randomized patients**
    - **Double-blind phase**
      - **PBO** (n=18)
        - Age, mean (SD) 61 (17)
        - Race, Caucasian, n (%) 7 (88)
        - **RIO** (n=19)
          - Age, mean (SD) 56 (13)
          - Race, Caucasian, n (%) 6 (67)
    - **All patients (n=37)**
      - Age, mean (SD) 61 (17)
      - Race, Caucasian, n (%) 7 (88)

- **Table 2: Changes from baseline to week 16 in primary and secondary efficacy end points**
  - **Characteristics (LS mean)**
    - NUB Reduction in NUB: The total number of active and indeterminate digital ulcers at an assessment.
    - Patient-reported outcomes (e.g., PROMIS, HDISS DU, Health Assessment Questionnaire Disability Index, VAS).

**CONCLUSION**

- **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.

**REFERENCES**

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- The BRIAN Scleroderma Research Consortium provided access to the data for the present study.

**DISCLOSURES**

- The authors declare no conflicts of interest.
- All 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 at baseline, and difficulty to recruit patients in the era of widespread use of PDE5 inhibitors.

**IMPLICATIONS**

- This trial provides evidence for the potential use of a vasodilator for treatment of digital ulcers in systemic sclerosis.
- Further studies are needed to confirm these findings and to explore the mechanism of action of riociguat in this setting.

**PROVENANCE**

- This is an investigator-initiated trial designed by the sponsor (Dinesh Khanna). The data were analyzed at the sponsor and the biostatistical and data management and reporting were performed by the biostatistics department of the sponsor.

**PRESENTED AT**

- ACR/ARHP Annual Meeting, November 2019, Atlanta, USA