Bosentan Prevents Occurrence But Does Not Speed Healing of Digital Ulcers in Patients with Systemic Sclerosis (SSc)

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Background and Rationale
- Progressive occlusive fibrinoid vasculopathy is the hallmark of systemic sclerosis (SSc).
- Vascular syndromes in SSc include pulmonary arterial hypertension (PAH), renal involvement, Raynaud’s phenomenon and ischemic digital ulcers.
- Digital ulcers occur in around 50% of patients and are responsible for pain, limitation of hand function and tissue loss.
- There are no effective therapies for digital ulcers.
- endothelin-1, its receptors, notably the ET-A receptor antagonizer, appeared to be a candidate.

Methods
- 188 subjects were studied in 41 centers in North America and Europe. Eligibility included a diagnosis of SSc and at least one recent active DTU. In subjects with more than one active DTU, a “cardinal” ulcers was identified by subject and investigator based on location, clinical impact and amenability to healing. Subjects received bosentan at 62.5 mg bid for 4 weeks then 125 mg bid for 20 to 32 weeks or placebo (PBO) in 1:1 blinded randomization. All DTUs were assessed at week 12 and at week 24.
- Co-primary endpoints were time to complete healing of the cardinal ulcer and the number of new DTUs that developed during 24 weeks of study. Secondary endpoints included SHAQ-DI, functional assessment in systemic sclerosis, and percent with complete healing (36.8% bosentan vs 39.3% PBO, p = 0.76).
- Overall bosentan was well tolerated and the safety profile was consistent with earlier RCTs of bosentan.

Results
- Subjects were well balanced between bosentan and PBO by age, gender, SSc classification, smoking history and concomitant medications. Total number of new ulcers over 24 weeks was 1.9 ± 0.2 on bosentan vs. 2.7 ± 0.3 on PBO (p = 0.033) and trended in favor of drug for “eating” at week 24 and “dressing” at week 12 (p = 0.034).
- Safety Overall bosentan was well tolerated and the safety profile was consistent with earlier RCTs of bosentan. 43% of adverse events were related to Raynaud’s phenomenon and ischemic digital ulcers.

Conclusions
- Bosentan appears effective in preventing the occurrence of digital ulcers after a placebo-controlled placebo-controlled (p = 0.034). SHAQ VAS scales were improved on bosentan for pain at week 12 (p = 0.034). SHAQ-DI was identified by subject and investigator based on location, clinical impact and amenability to healing. Subjects received bosentan at 62.5 mg bid for 4 weeks then 125 mg bid for 20 to 32 weeks or placebo (PBO) in 1:1 blinded randomization. All DTUs were assessed at week 12 and at week 24.
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REFERENCES

ACKNOWLEDGEMENT
The study was supported by a grant from Actelion Pharmaceuticals, Allschwil, Switzerland.