Trial in Progress: The Randomized, Double-Blind, Multicenter, Placebo-Controlled Phase 3 RESOLVE Trial Investigating the Efficacy of Voxelotor With Standard of Care in the Resolution of Leg Ulcers in Patients With Sickle Cell Disease

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BACKGROUND

- Sickle cell disease (SCD) is a heritable blood disorder caused by a point mutation in the β-globin gene.[1]
  - Polymerization of sickle hemoglobin (HbS) under deoxygenation is the major driver of SCD pathology.[2,3]
  - Due to the sickling of red blood cells, patients with SCD experience chronic hemolytic anemia and repeated episodes of vaso-occlusion, which lead to a systemic vasculopathy that clinically manifests as acute and chronic complications affecting multiple organ systems, including painful and debilitating leg ulcers.[1,3,4]
- Leg ulcers are a clinically overt expression of the underlying vasculopathy of SCD that can progress from epidermal skin loss to extensive tissue destruction and necrosis.[5]
  - Leg ulcers are almost exclusively found in patients with severe SCD genotypes (homozygous HbS [HbSS] or heterozygous HbS and beta-zero thalassemia [HbSβ^0]) and are rarely found in milder forms of SCD.[5]
- Leg ulcers are a marker of disease severity.[1,5]
  - Leg ulcers are associated with more-profound anemia and hemolysis in affected individuals.
  - Patients with SCD are at an increased risk of developing severe complications linked to hemolytic anemia, eg, pulmonary hypertension, renal disease, priapism, and retinopathy.
- The pain associated with leg ulcers is excruciating and distinctly different from the pain associated with vaso-occlusive crises.[5]
  - Formation of new ulcers is preceded by sharp pain, and the severity of the pain is independent of the size of the ulcer; intense and irregular pain, associated gait abnormalities, and lower limb deformities lead to physical and emotional impairment.[5]
  - Debilitating pain, immobility, and stigma negatively impact QOL and work productivity.[7]
- A qualitative study conducted with patients participating in another trial demonstrated that leg ulcers worsen physical function, lead to more pain interference in daily life, and negatively affect the social relationships of patients with SCD.[8]
  - Currently, there is no approved treatment for SCD-related leg ulcers.
  - The current standard of care for leg ulcers (supportive management) results in poor outcomes.
- The prevalence of leg ulcers among people with SCD is likely underestimated given the lack of registries and the lack of large prospective studies examining this complication.[5,7]
  - Current estimates of leg ulcers vary widely by geographic region: 43% in Brazil,[7] 30% in Jamaica,[9] 27% in Nigeria,[7] 19% in Ghana,[10] 13% in Sierra Leone,[7] 8% in Saudi Arabia,[9] and 1% to 5% in the United States.[5]
  - Among Americans with SCD, an estimated 14% to 18% may develop leg ulcers.[5]
- Voxelotor, a HbS polymerization inhibitor, is approved in the United States for the treatment of SCD in adults and pediatric patients aged ≥4 years, and in the European Union and the United Arab Emirates for the treatment of patients aged ≥12 years.[11,12]
- In a post hoc analysis of voxelotor-treated patients from the phase 3 HOPE study (NCT03036813), leg ulcers resolved within 24 weeks in 10 out of 14 patients and improved or resolved in 13 out of 14 patients by week 72. In the control arm, existing and new leg ulcers improved or resolved in 5 out of 8 patients by week 72.
  - The resolution of leg ulcers was associated with increases in Hb levels, reductions in markers of hemolysis, and greater Hb occupancy at 24 weeks in patients who received voxelotor.

OBJECTIVE

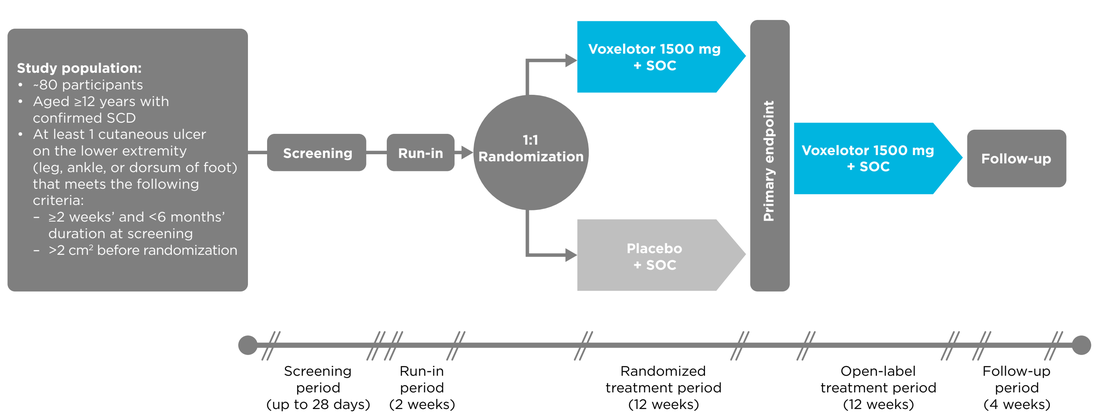
- To investigate the efficacy of voxelotor plus standard of care (SOC) in the resolution of leg ulcers in patients with SCD.

METHODS

- RESOLVE is an ongoing phase 3, randomized, double-blind, placebo-controlled, multicenter trial investigating the efficacy of voxelotor plus SOC in the resolution of leg ulcers in patients with SCD.
- Target enrollment is 80 patients aged ≥12 years from Nigeria, Kenya, and Brazil (**Figure 1**) with the following:
  - A confirmed diagnosis of SCD (HbSS or HbSβ^0)
  - ≥1 cutaneous ulcer on the lower extremity (leg, ankle, or dorsum of foot) that meets the following criteria:
    - ≥2 weeks' and <6 months' duration at screening
    - >2 cm^2 in area before randomization
- Participants with multiple ulcers are eligible for the study; to qualify as a target ulcer, the ulcer must meet the criteria above.
- After a 2-week run-in period, participants are randomized 1:1 to receive once-daily oral voxelotor 1500 mg or placebo in addition to SOC for 12 weeks.
- After the randomized treatment period, all participants are eligible to receive open-label voxelotor 1500 mg plus SOC for 12 weeks (**Figure 2**).

Figure 1. Participating Countries in the RESOLVE Study

Figure 2. RESOLVE Study Design, Population, and Timeline



SCD, sickle cell disease; SOC, standard of care.

OUTCOMES

- The primary objective of the study is to assess the efficacy of voxelotor plus SOC compared with placebo plus SOC on leg ulcer healing, measured by the proportion of patients with resolution of target ulcer(s) in each treatment group by week 12.
  - Resolution of skin ulcers is defined as skin re-epithelialization confirmed at 2 consecutive study visits 2 weeks apart during the 12-week randomized treatment period.
- Key secondary endpoints include:
  - Days to resolution of target ulcer(s) up to week 12
  - Change from baseline in total surface area of target ulcer(s) at week 12
  - Incidence of new ulcers by week 12
- The safety objective of RESOLVE is to assess adverse events (AEs), clinical laboratory tests, physical examinations, vital signs, and other clinical measures (eg, discontinuations due to AEs, dose reductions) among voxelotor-treated participants compared with those given placebo.
- Participants will continue to be followed for efficacy and safety through at least the endpoint visit (week 12) regardless of treatment discontinuation.

DISCUSSION

- RESOLVE is an ongoing phase 3, randomized, double-blind, placebo-controlled, multicenter study.
  - Results from the RESOLVE study will further guide clinicians and patients regarding the clinical use of voxelotor for the treatment of leg ulcers in patients with SCD.[a]
- Participants will have the option to enroll in a separate open-label extension study after the 24-week treatment period.

[a]For questions or inquiries regarding this study, please contact voxelotorstudies@gbt.com.

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DISCLOSURES

- **Caterina P. Minniti:** Consultant: Global Blood Therapeutics, Novartis, Novo Nordisk, Roche, Forma, Agios, Sangamo, Chiesi, Emmaus Lifescience, Sanguine Biosciences. **Shannon Bradley:** Biostatistics consultant: Global Blood Therapeutics. **Jennifer Doss:** Employee, equity ownership: Global Blood Therapeutics. **David Purdie:** Employee: Global Blood Therapeutics. **Carolyn Hoppe:** Employee, equity ownership: Global Blood Therapeutics. **Andrew Crouch:** Consultant: Global Blood Therapeutics.
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