Compassionate-use Experience With Voxelotor (GBT440) for Patients With Severe Sickle Cell Disease (SCD) and Life-Threatening Comorbidities

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Disclosures

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Background

- Current treatments of SCD inadequately control disease-related complications and do not address the primary pathogenesis of SCD, leaving a high unmet need for more effective treatment options[1]
- Patients with severe SCD can face systematic exclusion from ongoing clinical trials of investigational agents for SCD[2]
- The FDA provides expanded access—"compassionate use"—of an investigational drug for treatment of patients with serious or immediately life-threatening diseases/conditions who lack therapeutic alternatives[3]

FDA, US Food and Drug Administration.

1. Eaton WA, Bunn HF. Treating sickle cell disease by targeting HbS polymerization. *Blood*. 2017;129(20):2719-2726. 2. ClinicalTrials.gov. https://clinicaltrials.gov. Trials: NCT03036813, NCT03492931, NCT03285178, NCT01245179. Accessed May 10, 2018. 3. Investigational New Drug Application, Subpart I–Expanded Access to Investigational Drugs for Treatment Use. (Food and Drugs, 21 C.F.R. §312.300–312.320. 2009.

Key FDA Requirements for Expanded Access for Life-Threatening Conditions

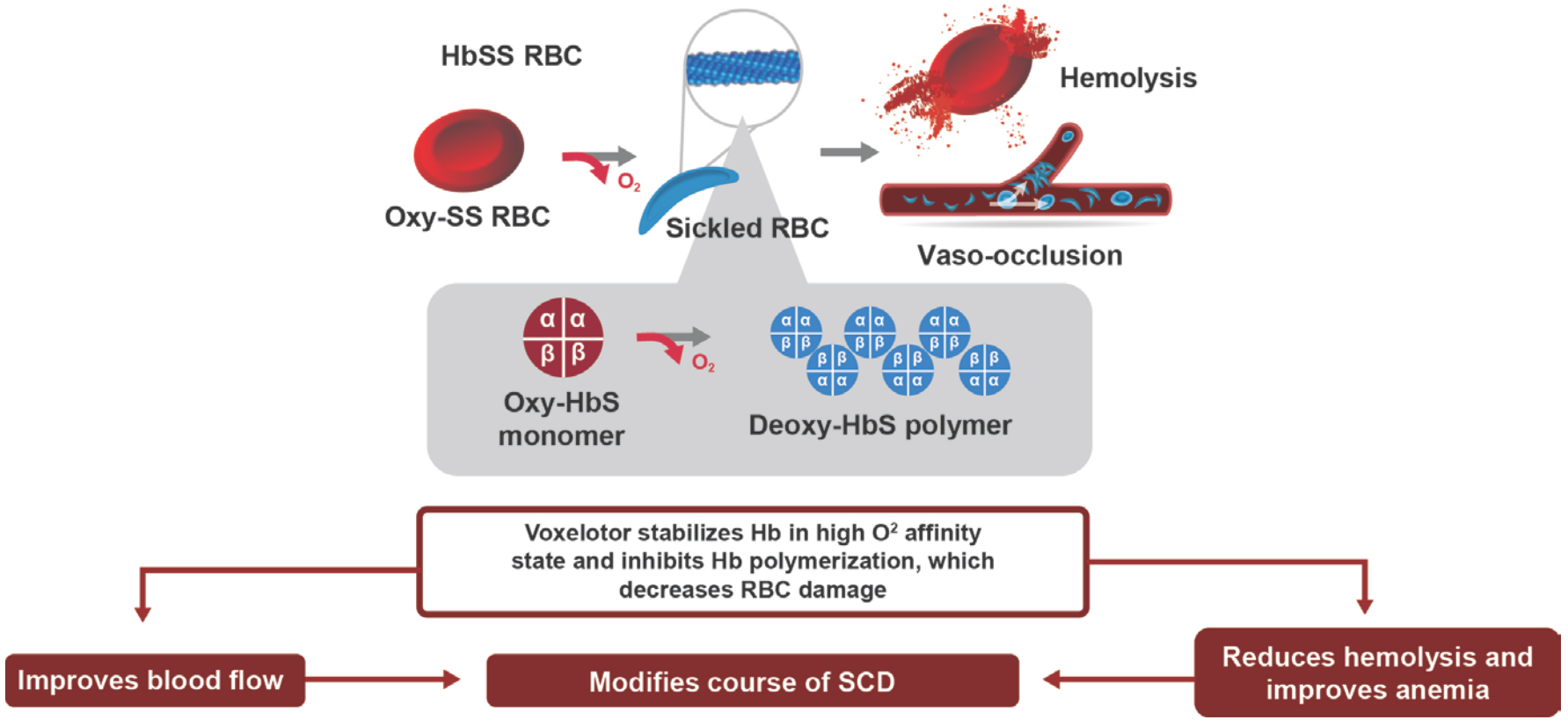
- No comparable or satisfactory therapy available to treat the patient's disease or condition
- Must be a serious and immediately life-threatening condition
- Potential benefit justifies potential risk
- Patient's inability to obtain the IND under another IND application or to participate in a clinical trial
- Emergency IND – requires physician; considers product may be urgently needed for the patient's serious or life-threatening condition

IND, investigational new drug.

FDA. Investigational New Drug Application, Subpart I–Expanded Access to Investigational Drugs for Treatment Use. (Food and Drugs, 21 C.F.R. §312.300–312.320. 2009.

Voxelotor Clinical Hypothesis: Upstream Interruption of HbS Polymerization With Potential to Modify Disease

Voxelotor–first-in-class, oral, once-daily therapy that modulates the affinity of hemoglobin for oxygen and prevent sickle hemoglobin polymerization



Deoxy, deoxygenated; Hb, hemoglobin; HbS, sickle hemoglobin; O_2, oxygen; oxy, oxygenated; RBC, red blood cell; SS, sickle cell anemia.

GBT Voxelotor Compassionate Use Activity

- Patient treatment begun between May 2016 and June 2017
- All patients had end-stage SCD with multiple organ injury, predicting high risk of death
  - End-stage renal disease in SCD
  - Acute chest syndrome
  - Pulmonary hypertension/diastolic dysfunction
  - History of acute anemia
  - Advanced age
  - Low oxygen saturation
  - Frequent pain crisis

Patient Disposition and Characteristics

- 7 patients: 4 females and 3 males
- Treatment duration ranged from 6 to 17 months
- Key comorbidities
  - 5 patients had frequent transfusions
  - 4 patients had severe fatigue
  - All patients had iron overload
- Patient C was hospitalized twice with multiorgan failure and coma in the 18 months prior to treatment
- Patients A and E required continuous supplemental oxygen therapy

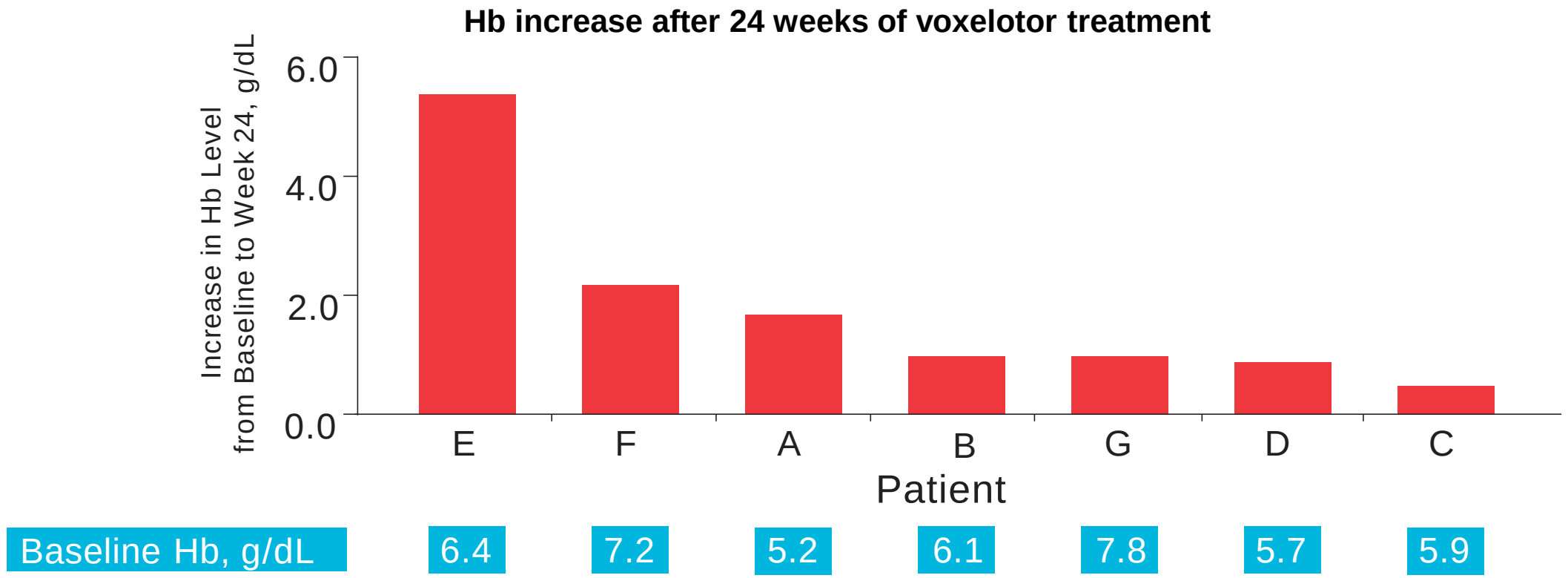
	Patient						
	A	B	C	D	E	F	G
Age	67	66	44	53	38	50	22
Gender	M	F	M	F	M	F	F
Type	SS	SS	Sβ° thal	SS	SS	SS	SS
Frequent transfusion		X	X	X	X	X	
Refractory to transfusion	X						
Severe fatigue	X			X	X	X	
Iron overload	X	X	X	X	X	X	X
Chronic oxygen supplementation	X				X		
Progressive severe renal dysfunction		X					
Multiorgan failure			X				
Treatment (months)	17	16	7	15	6	6	6

Sβ^0 thal, sickle beta zero thalassemia.

Clinical and Laboratory Efficacy

Increased Hb in Patients With Severe Disease

- Hb values increased rapidly in all patients, with increments ranging from 0.5 to 5.4 g/dL at 24 weeks
- Hb values increased by ≥1 g/dL in 5 of 7 patients

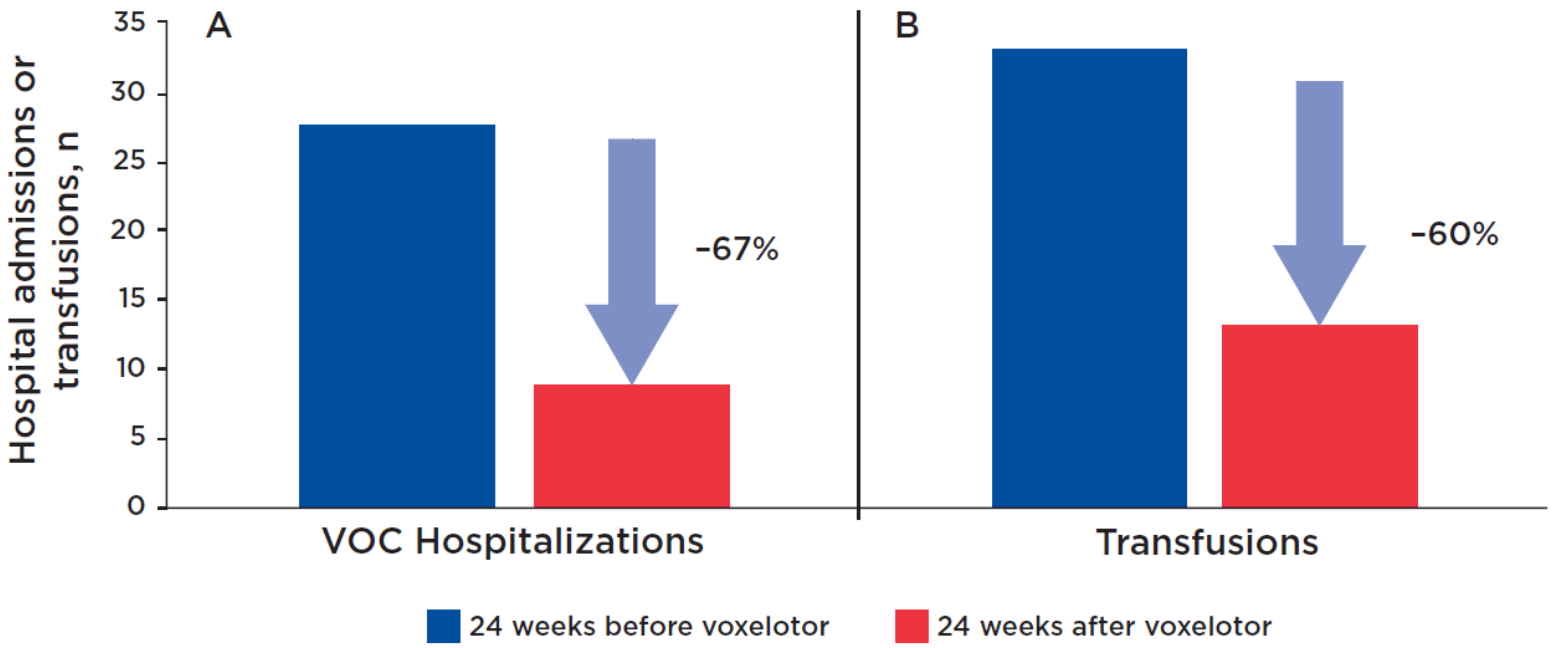


Clinical and Laboratory Efficacy (cont'd)

Large Reductions in VOC Hospitalizations and RBC Transfusions

- In the 24 weeks before and after voxelotor treatment
  - Total hospitalizations for VOC pain decreased by 67% (from 28 to 9, respectively)
    - Per-patient hospitalizations ranged from 2 to 5
  - Total RBC transfusions decreased by 60% (from 33 to 13, respectively)
    - 6 of 7 patients received transfusions before voxelotor, whereas 2 of 6 received no transfusions after voxelotor[a]

Total hospital admissions for VOC pain and total RBC transfusions 24 weeks before and after voxelotor treatment



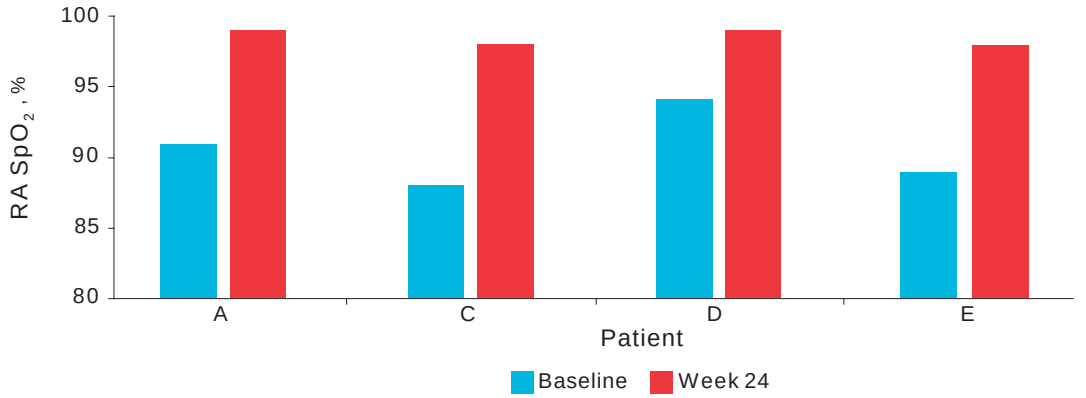
VOC, vaso-occlusive crisis.

[a]Patient A was alloimmunized to RBCs to the point of being refractory to any transfusion.

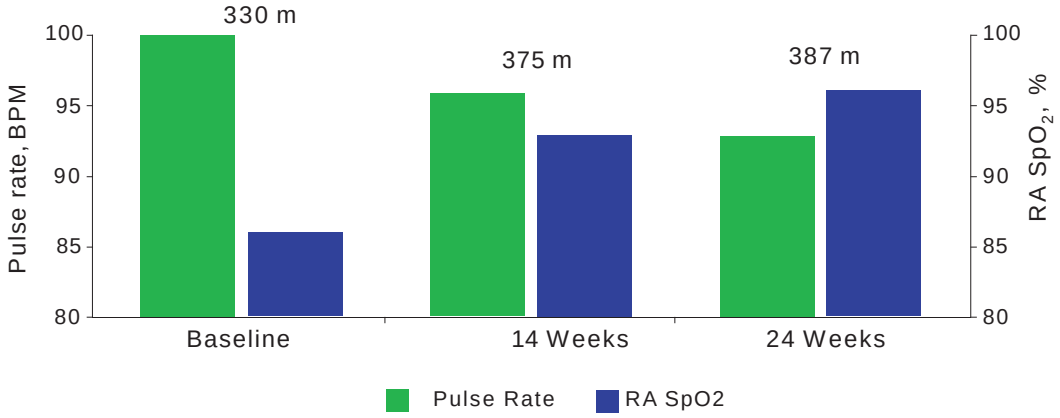
Clinical and Laboratory Efficacy (cont'd)
Room Air Oxygen Saturation

- 4 patients had low RA SpO_2 <95% at baseline that improved to 98%-99% with voxelotor treatment
  - Patients A and E no longer required continuous supplemental oxygen
- Patient A, who was initially receiving continuous supplemental oxygen, had a 6-minute walk test at baseline and again after 14 and 24 weeks of voxelotor treatment
  - Postwalk pulse rate and RA SpO_2 improved steadily over the course of treatment

RA SpO_2 after 24 weeks of voxelotor treatment



Voxelotor treatment and 6-minute walk test in patient A

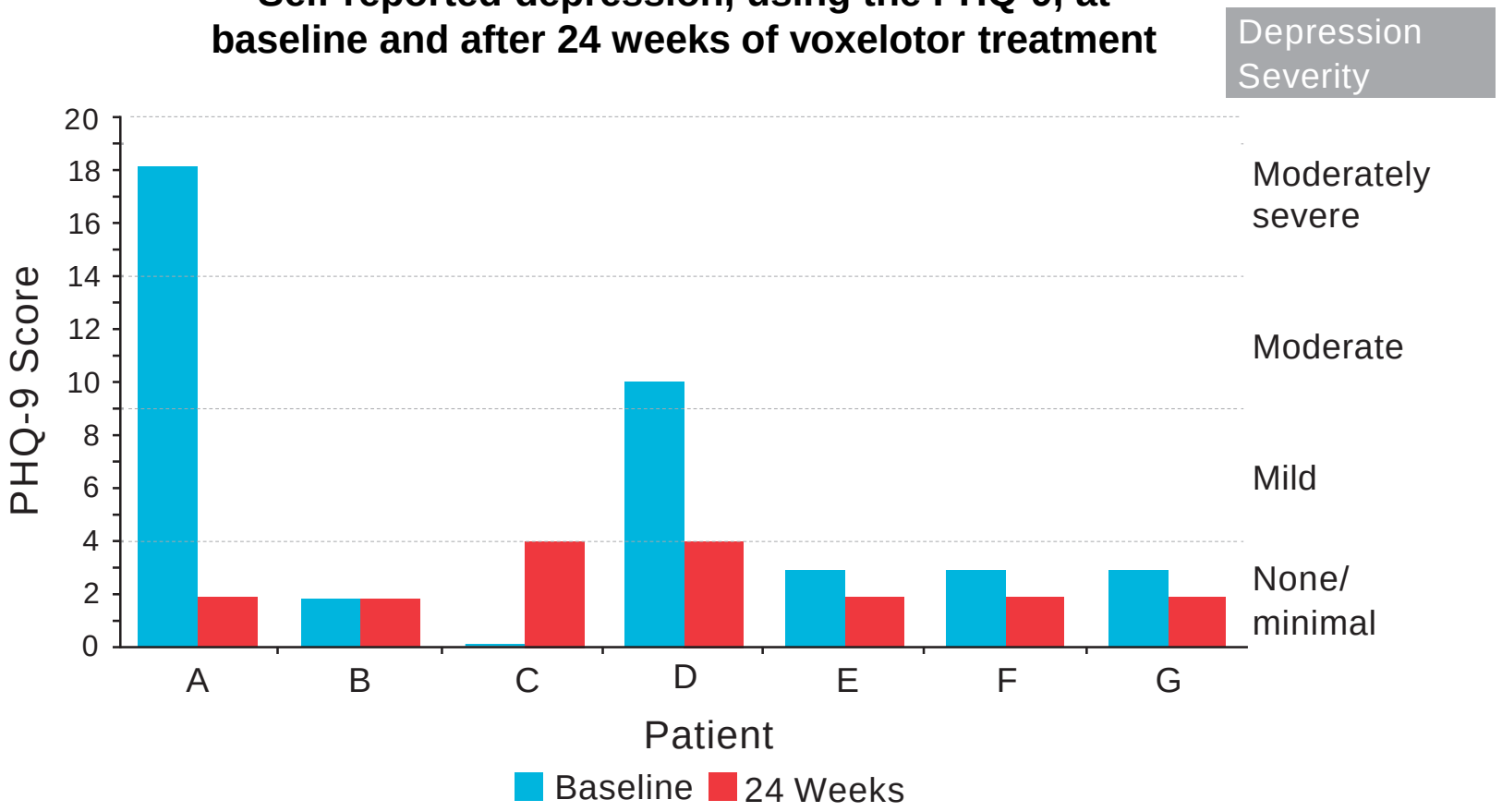


BPM, beats per minute; RA, room air; SpO_2, oxygen saturation.

Clinical and Laboratory Efficacy (cont'd)
Patient-Reported Outcomes

- At baseline, by the PHQ-9 scale
  - Patient D had moderate depression
  - Patient A had moderately severe depression
  - 5 patients had no or minimal depression
- After 24 weeks of treatment with voxelotor, PHQ-9 scores improved in patients A and D
  - Patient A and D showed no or minimal depression

Self-reported depression, using the PHQ-9, at baseline and after 24 weeks of voxelotor treatment



PHQ-9, Patient Health Questionnaire 9-item.

Safety Summary

- Voxelotor was well tolerated for up to 17 months at a dose of 900 mg, with no dose reductions or discontinuations
- The dose for patient A was increased to 1500 mg, which caused grade 2 diarrhea that resolved with a return to the 900-mg dose. The 1500-mg voxelotor dose produced no problems in any other patient
- Patient F had transient grade 1 diarrhea at the 900-mg dose that resolved with no treatment change
- No voxelotor-related serious adverse events occurred

Patient Deaths

- Patients B and C, each with extensive preexisting end-organ injury, died after starting voxelotor treatment
- The treating physician deemed both deaths unrelated to voxelotor treatment
- Patient B’s long-standing decline in renal function finally required hemodialysis several months into voxelotor treatment. Progressive hepatic failure from massive iron overload became critical at about month 15, and the patient died at month 16
- Patient C experienced 3 episodes of multiorgan failure (2 with coma) over the 18 months prior to voxelotor treatment. He substantially improved with voxelotor treatment to the point that after 7 months he was able to engage in vigorous physical activity (eg, rock climbing). However, he developed an SCD pain crisis that deteriorated into multiorgan failure. He deteriorated over 3 days and died after a failed cardiac resuscitation

Conclusions

- In this uncontrolled experience in 7 patients with severe SCD who were not eligible for the HOPE study, voxelotor administered via compassionate use demonstrated large improvements in anemia and hemolysis, including in patients with lower baseline Hb than studied in clinical trials to date
- Voxelotor also substantially improved a variety of other clinical and patient-reported parameters, including hospital admissions related to VOC, frequency of blood transfusions, daily pain, overall well-being, and depression
- These data are suggestive of meaningful improvement in clinical events and symptoms in patients with severe SCD and support ongoing investigation in controlled clinical trials to confirm the benefits of voxelotor in a broad range of patients with SCD

HOPE, **H**emoglobin **O**xygen Affinity Modulation to Inhibit HbS **P**olym**E**rization.

Acknowledgments

- The authors thank all the patients, families, caregivers, research nurses, study coordinators, and support staff who contributed to this study

Backup Slides

Patient Deaths

Patient B	Patient C
• Hb values: 4.5–6 g/dL • Chronic RBC transfusions every 6–8 weeks • Frequent hospitalizations for VOC • Chronic kidney disease • Transfusional iron overload with hepatopathy • Multiple RBC alloantibodies	• Hb values: 4–6 g/dL • Frequent multiunit RBC transfusions • Frequent hospitalizations for VOC • 3 episodes of multiorgan failure (2 with coma) over the 18 months prior to voxelotor treatment • Iron overload • Pulmonary artery hypertension • Chronic renal dysfunction
Voxelotor Experience	**Voxelotor Experience**
• 16 months of treatment (3-month interruption with start of dialysis) • Transfusions reduced by half • VOC hospitalizations reduced by half • Improved well-being and QoL • Death in October 2017 due to hepatic failure superimposed on renal failure	• Improved well-being and QoL • Transfusions reduced by 67% • VOC hospitalizations reduced by 60% • Died in December 2016 after a failed resuscitation for cardiac arrest

Hb, hemoglobin; QoL, quality of life; RBC, red blood cell; VOC, vaso-occlusive crisis.