# Compassionate-use Voxelotor (GBT440) for up to 2 Years in Patients With Severe Sickle Cell Disease and Life-Threatening Comorbidities

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# Disclosures

- Dr. Bridges is an employee of Global Blood Therapeutics and has equity in the company
- This study was supported by Global Blood Therapeutics

# Background

- Current treatments SCD
  - inadequately control disease-related complications
  - do not address the primary pathogenesis of SCD
  - leave a high unmet need for more effective treatment options[1]
- Patients with severe SCD are routinely excluded from 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]

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.

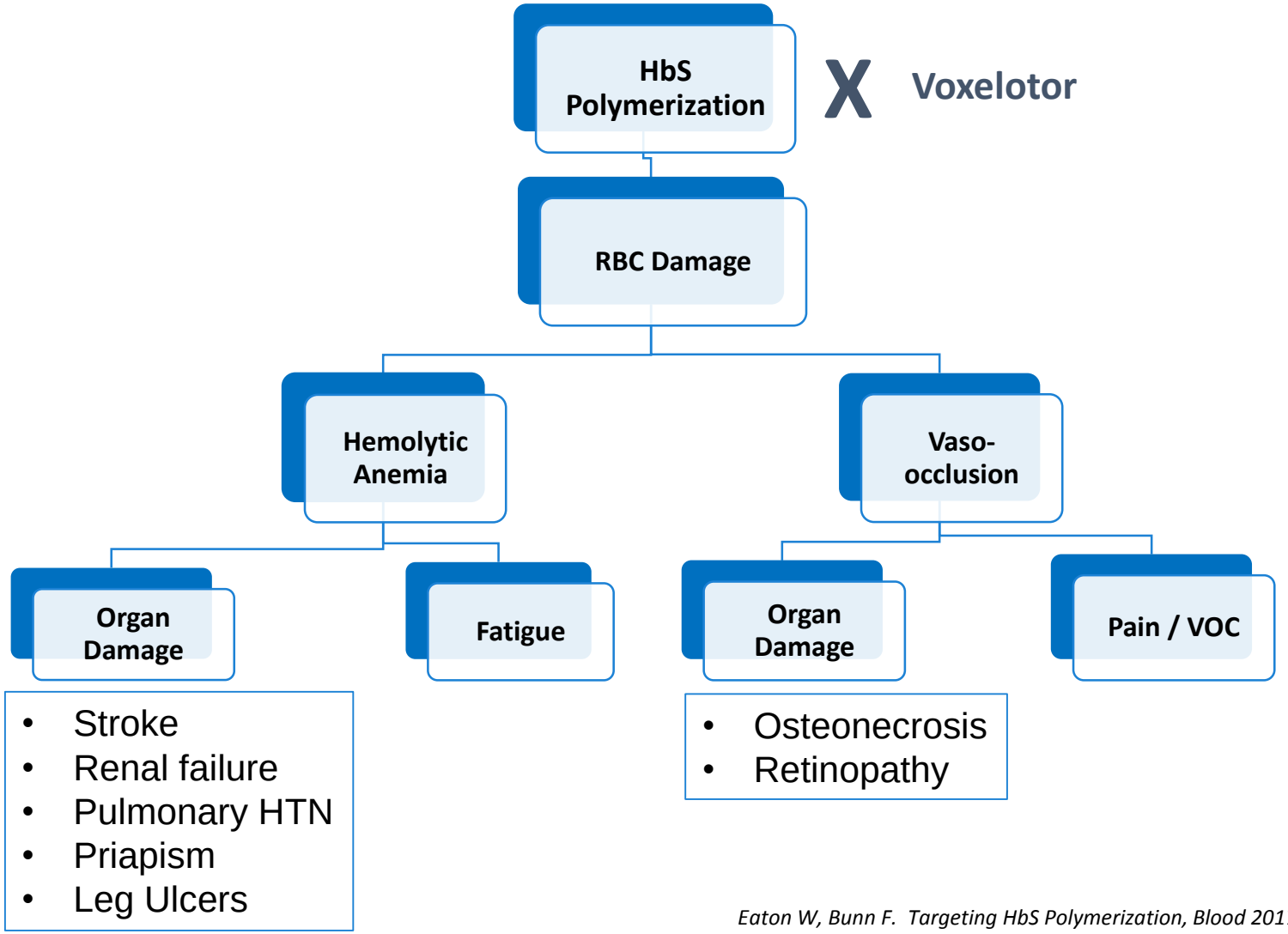
# Key FDA Requirements for Expanded Access for Life-Threatening Conditions

- No comparable or satisfactory therapy exists for the patient's disease or condition
- Conditions must be serious and immediately life-threatening
- Potential benefit justifies potential risk
- The investigational drug is unavailable under another IND or clinical trial

IND, investigational new drug.

US Food & Drug Administration. 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 Interruption of HbS Polymerization Could Modify Disease






*Eaton W, Bunn F. Targeting HbS Polymerization, Blood 2017, Kato JCI 2017*

# GBT Voxelotor Compassionate Use Activity

- Patient treatment begun between May 2016 and June 2017
- All had advanced SCD with multiple organ injury predicting high risk of death and one or more of the following complications:
  - End stage renal disease in SCD
  - Recurrent multi-organ failure
  - Pulmonary hypertension/diastolic dysfunction
  - History of severe anemia
  - Advanced age
  - Low $O_2$ saturation
  - Frequent pain crises

# Patient Disposition and Characteristics

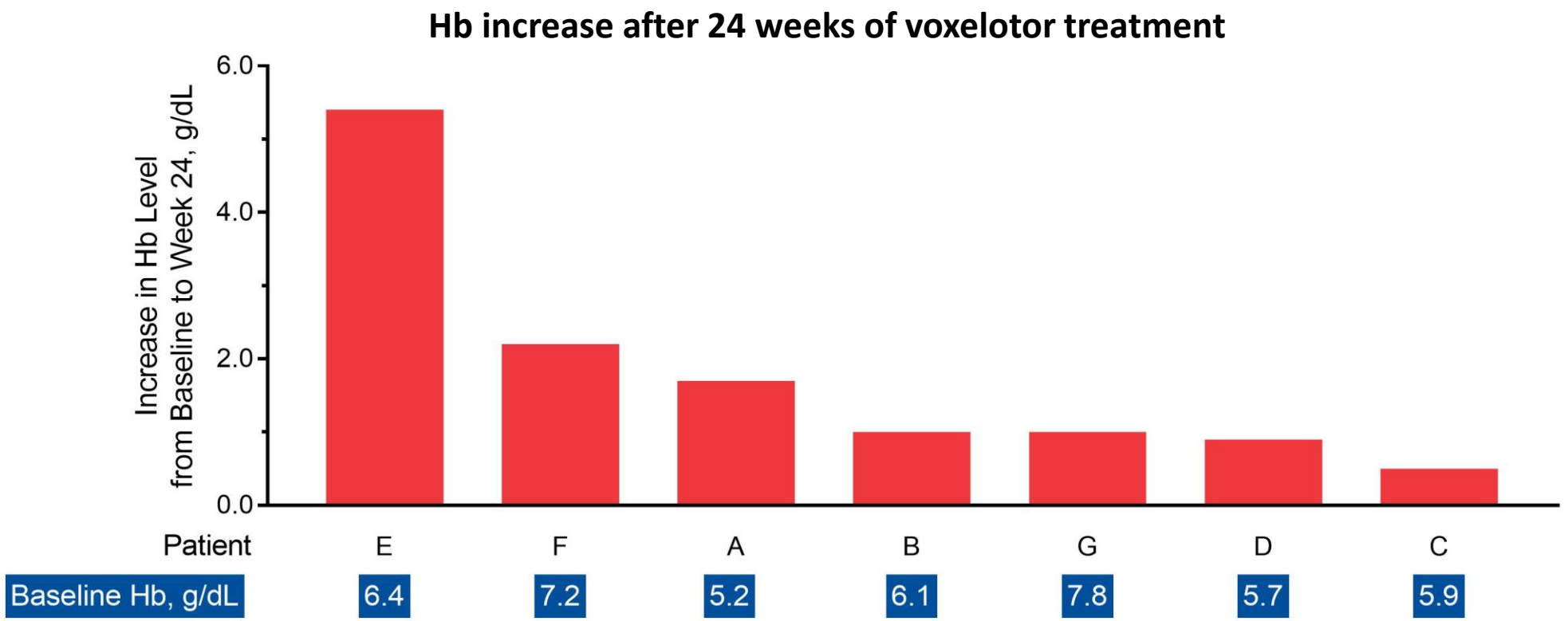
- 7 patients: 4 females and 3 males
- Treatment duration ranged from 6 months to 2 years
- Key comorbidities
  - 5 patient had frequent transfusions
  - 4 patients had severe fatigue
  - All patients had iron overload
- Patient C hospitalized twice with multiorgan failure and coma in the 18 months prior to treatment
- Patients A and E required continuous supplemental $O_2$ therapy

| Patient | A | B | C | D | E | F | G |
|---|---|---|---|---|---|---|---|
| Age | 68 | 66 | 44 | 53 | 38 | 50 | 22 |
| Gender | M | F | M | F | M | F | F |
| Type | SS | SS | $S\beta^0$ 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 $O_2$ supplementation | X | | | | X | | |
| Progressive severe renal dysfunction | | X | | | | | |
| Multi-organ failure | | | X | | | | |
| Treatment (months) | 24 | 16 | 7 | 15 | 6 | 6 | 6 |

$O_2$, oxygen; $S\beta^0$ thal, sickle beta zero thalassemia; SS, sickle cell anemia.

# Voxelotor Produced Substantial Hb Rises at 24 weeks

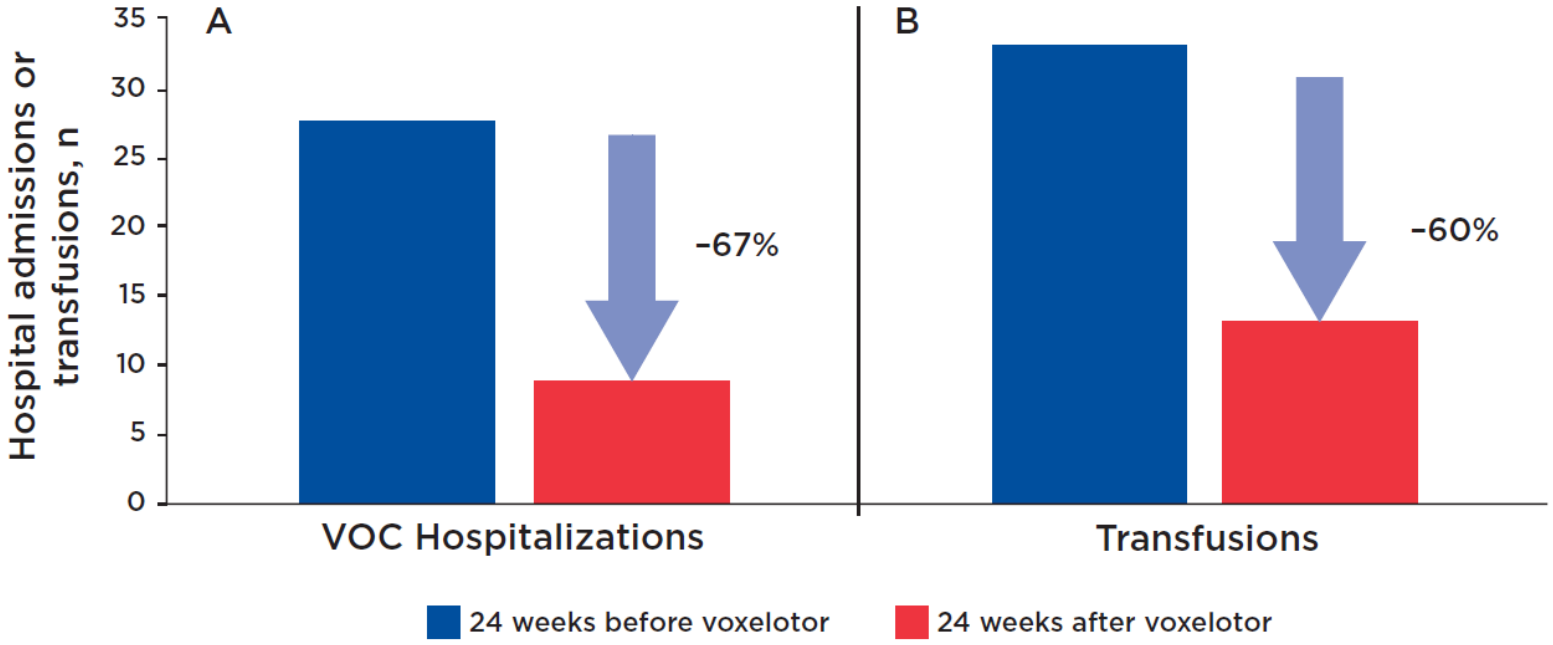
- Hb values increased rapidly in all patients, with increments ranging from 0.5 to 5.4 g/dL at 24 weeks
- Hb values increased by ≥1 g/dL in 5 of 7 patients



# Voxelotor Lowered Hospitalizations for VOC and Number of 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, while 2 of 6 received no transfusions after[a]

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

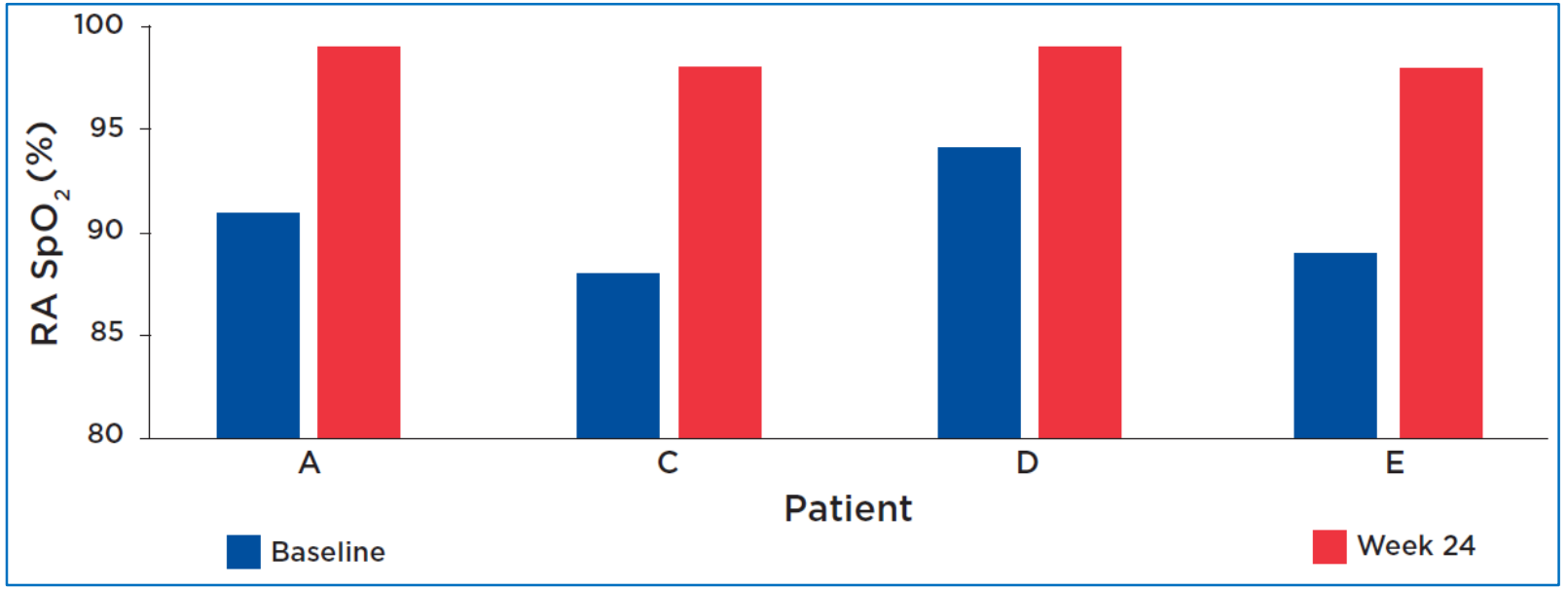



[a]Patient A, who was alloimmunized to RBCs to the point of being refractory to any transfusion.

# Voxelotor Improved Oxygenation

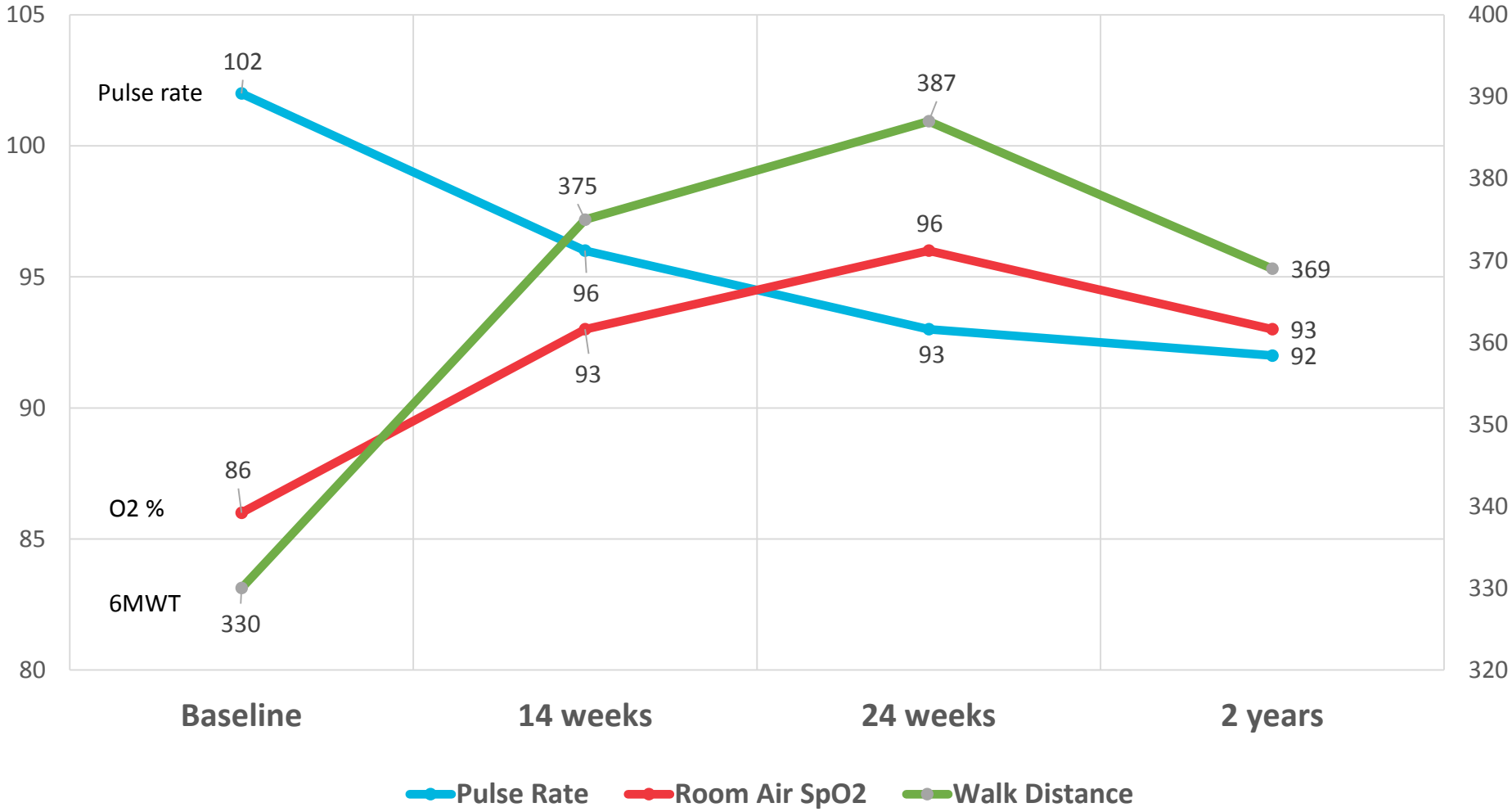
- 4 patients had low room air oxygen saturations of <95% at baseline that improved to 98%–99% with voxelotor treatment
  - Patients A and E no longer required continuous supplemental oxygen

Room air $O_2$ saturation after 24 weeks of voxelotor treatment.




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

# Voxelotor Improved 6-minute Walk Test in Patient A for 2 Years



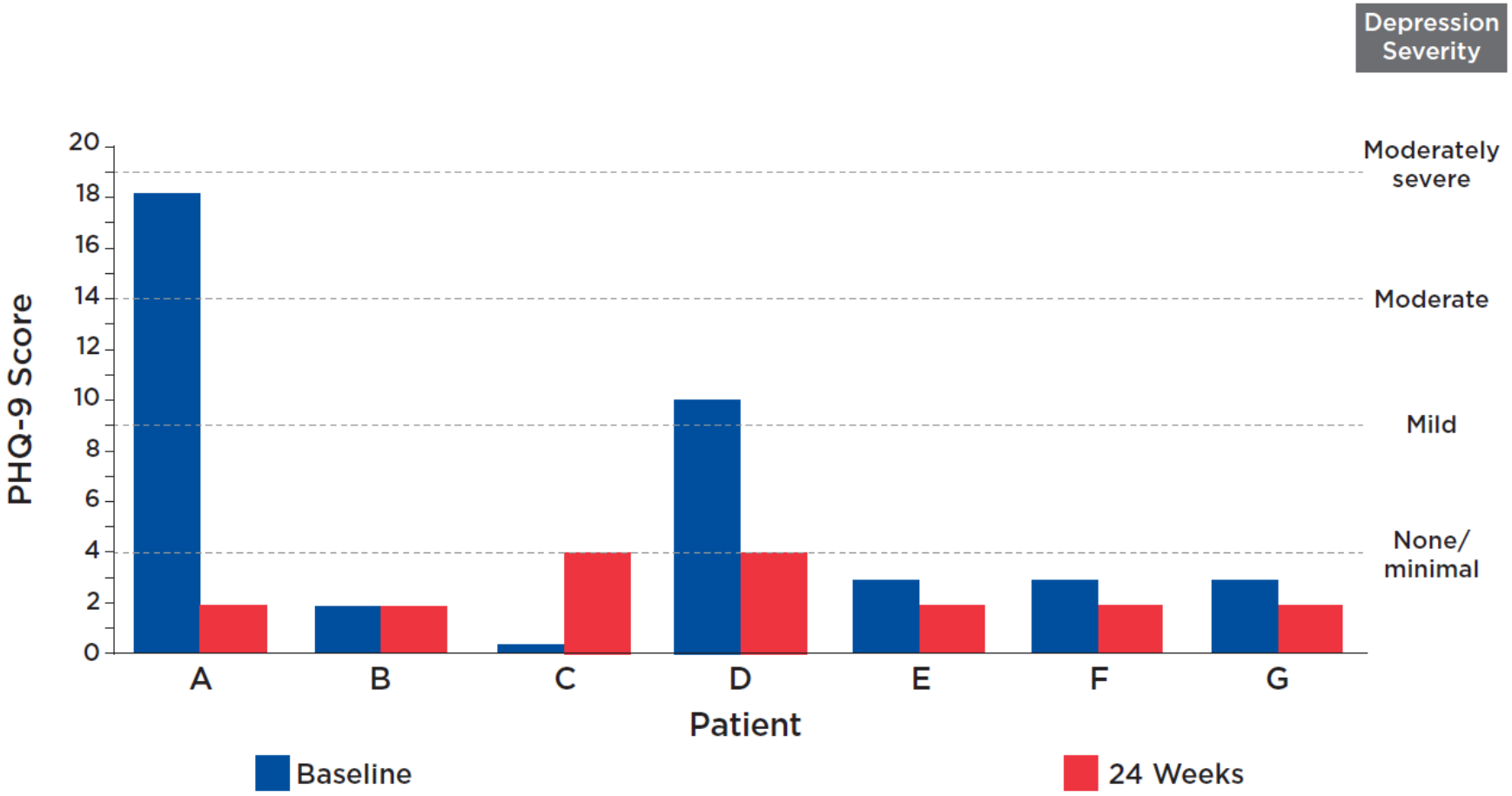

- Patient A, who was initially on continuous supplemental oxygen, had a 6-minute walk test at baseline and again after 14, 24 and 48 weeks of voxelotor treatment
- Post-walk pulse rate and room air $SpO_2$ improved rapidly and was maintained

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

# Voxelotor Improved Patient-Related Outcome

- 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 showed no or minimal depression
  - Patient D showed only mild depression

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




PHQ-9, Patient Health Questionnaire-9.

# Safety Summary

- Voxelotor was well-tolerated for up to 17 months at a dose of 900 mg with no dose reductions or discontinuations
- Patients B and C, each with extensive preexisting end-organ injury, died after starting voxelotor treatment due to end organ failure
- 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

# Conclusions

- In 7 patients with severe SCD who were not eligible for the HOPE study, voxelotor administered by compassionate use substantially improved a variety of clinical, laboratory, and patient-reported parameters, including:
  - Hb levels, hospital admissions related to VOC, frequency of blood transfusions, daily pain, overall well-being, and depression
- Controlled clinical trials are needed to confirm the benefits of voxelotor in patients with severe SCD

# Acknowledgments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