Rheological Impact of GBT1118 Cessation on a Sickle Cell Mouse Model

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Disclosures

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• Nothing to disclose

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• Nothing to disclose

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• Research funding: Global Blood Therapeutics, Emmaus, Novartis
Voxelotor Safety Concern: What Happens When You Stop the Drug?

- Average rise in Hb is 1 g/dL on voxelotor.
- Any rise in Hb increases blood viscosity, but SCD blood is more viscous than normal blood for every unit of hemoglobin.
- Voxelotor will be cleared within 72 hours, but the extra HbS will remain for 14 to 20 days.
  - Is there a higher risk of viscosity-related SCD complications in that window?
- **Plan:** Give GBT1118 to Townes SCD mice for 7 days.
  - Measure viscosity and deformability on and off drug.
  - Determine if viscosity rises or hematocrit to viscosity ratio (HVR) falls with cessation of drug.

Hb, hemoglobin; HbS, sickled hemoglobin; SCD, sickle cell disease.
Hemoglobin Rise on GBT1118

**Figure 1.**

A. Expected rise and fall of total hemoglobin with GBT1118 treatment and its withdrawal.

B. Drug Hb occupancy decline off GBT1118.

*P<0.05; **P<0.001.

Hb, hemoglobin
Viscosity/HVR Effects

A. At a shear rate of 45 s⁻¹, modeling venous circulation, there is no significant change in viscosity from baseline.

B. At a shear rate of 225 s⁻¹, modeling arterial circulation, viscosity on drug declines from baseline on treatment and 24 hours off drug. There is no significant rise in viscosity 48 hours off drug compared to baseline.

C. At an HVR at 45 s⁻¹, oxygen carrying capacity increased 24 hours off drug.

D. At an HVR at 255 s⁻¹, oxygen carrying capacity increased on drug and 24 hours off drug. There was no significant decline in HVR 48 hours off drug compared to baseline at 225 or 45 s⁻¹ HVR.

***P<0.0001; **P<0.005; *P<0.05.

HVR, hematocrit to viscosity ratio.
**Deformability Effects**

![Graphs showing deformability effects](image)

**Figure 3.**

A. RBC deformability when deoxygenated rises on drug and declines but remains above baseline up to 48 hours off drug.  
B. RBC deformability when oxygenated rises on drug.  
C. POS drops on drug and returns to baseline 48 hours off drug.

***P<0.0001; **P<0.05.

EI<sub>max</sub>, maximum elongation index; EI<sub>min</sub>, minimum elongation index; POS, point of sickling; RBC, red blood cell.
Conclusions

On GBT1118
- Hb rose; $E_{I_{\text{min}}}$ and POS improved.
- Viscosity did not rise significantly.
- HVR rose, indicating better quality Hb to offset rise in Hb and improved oxygen carrying capacity.

Off GBT1118
- Hb dropped very rapidly.
- Viscosity was higher at 48 hours post drug than on drug, but not higher than baseline.
- Deformability, particularly $E_{I_{\text{min}}}$, remained improved after drug was cleared, and POS returned to baseline.

$E_{I_{\text{min}}}$, minimum elongation index; Hb, hemoglobin; HVR, hematocrit to viscosity ratio; POS, point of sickling.
Acknowledgments

- This work was supported by Global Blood Therapeutics.