## Cerebral Blood Flow In Adolescents With Sickle Cell Anemia Receiving Voxelotor

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**Background:** Oxygenated sickle hemoglobin (HbS) does not polymerize; therefore, increasing oxygen affinity to HbS is a therapeutic strategy for sickle cell anemia (SCA; HbSS and HbSβ0thalassemia), and voxelotor (GBT440) is a first-in-class, small molecule that increases the affinity of hemoglobin for oxygen. It has been postulated that increasing hemoglobin-oxygen affinity could limit oxygen offloading from hemoglobin, thus impairing tissue oxygenation which could lead to an increase in cerebral blood flow and potential risk of stroke. This study used MRI techniques to evaluate cerebrovascular hemodynamics to inform on cerebral oxygenation with voxelotor therapy.

**Aims:** To assess effects of voxelotor on grey matter cerebral blood flow (CBF) in children with SCA.

**Methods:** This was a St. Jude Children's Research Hospital (St. Jude) investigator-initiated, ancillary study of children enrolled in the HOPE-KIDS1 (NCT02850406) trial. Study activities were approved by the St. Jude IRB and all participants provided documentation of informed consent. Participants underwent two non-sedated functional magnetic resonance imaging with angiography (MRI/MRA) evaluations, once prior to receiving voxelotor and again following multiple doses (Table). Time resolved phase-contrast (PC) MR imaging was used to measure CBF during multiple phases of the cardiac cycle at several anatomic locations, including the internal carotid arteries and anterior, middle and posterior cerebral arteries, and arterial spin labeling (ASL) sequences utilizing a multi-channel head coil in a 3T scanner were performed.

**Results:** Preliminary data on three patients are available. All three participants (Table) were being treated with a stable dose of hydroxyurea and had normal transcranial doppler velocities upon study entry. As per the HOPE-KIDS1 study design, two received voxelotor at 900 mg per day and one received 1500 mg per day. Baseline MRI/MRA exams were normal in two participants and one had silent cerebral infarcts without vasculopathy. Generally, participants had higher hemoglobin levels and decreased hemolysis while receiving voxelotor. Two patients had lower global CBF while receiving voxelotor and the third showed essentially no change in CBF. Repeat MRI/MRAs showed no new or evolving areas of ischemia and EPO levels did not increase over time.

| Cases | 1 | | 2 | | 3 | |
|---|---|---|---|---|---|---|
| Genotype | HbSβ$^0$thal | | HbSS | | HbSS | |
| Age, y | 14.6 | | 12.8 | | 14.3 | |
| Sex | Male | | Female | | Female | |
| Height, cm | 167.7 | | 154.8 | | 166 | |
| Weight, kg | 58.9 | | 39.4 | | 60.3 | |
| Hydroxyurea dose, mg/kg | 26.2 | | 30.2 | | 26.5 | |
| Voxelotor dose, mg/kg | 900 | | 900 | | 1500 | |
| Evaluation point | 0 | 1 | 0 | 1 | 0 | 1 |
| Time on study, days | -4 | 36 | -4 | 80 | 0 | 56 |
| Cerebral Blood Flow mL/100g/min | 96.0 | 92.0 | 134 | 108 | 95.2 | 95.4 |
| Laboratory Parameters | | | | | | |
| Hemoglobin, g/dL | 11.3 | 11.4 | 7.4 | 8.0 | 10.6 | 11.6 |
| Mean Corpuscular Volume, fL | 79.4 | 78.1 | 94.0 | 83.4 | 134.9 | 132.1 |
| Fetal Hemoglobin, % | 5.5 | -- | 4.2 | -- | 24.4 | -- |
| Erythropoietin, mU/mL | 47 | 44 | 129 | 135 | 267 | 196 |
| Absolute Reticulocyte Count, cells x10$^9$/L | 227 | 306 | 330 | 306 | 163 | 142 |
| Lactate Dehydrogenase, units/L | 476 | 479 | 688 | 625 | 455 | 406 |
| Bilirubin, mg/dL | 2.4 | 2.5 | 2.5 | 1.7 | 1.8 | 1.3 |

**Summary/Conclusion:** Vasodilatory autoregulation of the cerebral vasculature enables a rapid and effective mechanism to titrate blood flow based on metabolic demand; increasing cerebral blood flow to offset impaired tissue oxygenation (Guilliams, K. Stroke 2019). In our small cohort of adolescents with SCA, the lack of increase in CBF after treatment with voxelotor suggests that there is no impairment in oxygen unloading to brain tissue. In fact, these preliminary findings of decreasing CBF with rising hemoglobin levels in two patients suggest improved oxygen delivery to the brain. Further study on the effects of voxelotor on cerebral hemodynamics and oxygen delivery is warranted.