



## The 65th ASH Annual Meeting Abstracts

## ORAL ABSTRACTS

## 114. SICKLE CELL DISEASE, SICKLE CELL TRAIT AND OTHER HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIAS: CLINICAL AND EPIDEMIOLOGICAL

**Neurocognitive Improvement with Hydroxyurea Therapy in Children with Sickle Cell Anemia in Uganda: Interim Analysis at Month 18**

Shubaya Kasule Naggayi, MSc<sup>1,2</sup>, Dennis Kalibala<sup>2</sup>, Robert Opoka, MBChB, PhD<sup>3,4</sup>, Caterina Rosano, MD MPH<sup>5</sup>, Deogratias Munube, MD<sup>4</sup>, Phillip Kasirye, MD<sup>4</sup>, Ezekiel Mupere, MD PhD<sup>4</sup>, Vincent Mboizi<sup>2</sup>, John Ssenkusu, PhD<sup>6</sup>, Nancy S. Green, MD<sup>7</sup>, Richard Idro, PhD<sup>4</sup>, Paul Bangirana, PhD<sup>8</sup>

<sup>1</sup> Makerere University College of Health Sciences, Kampala, Uganda

<sup>2</sup> Global Health Uganda, Kampala, Uganda

<sup>3</sup> Department of Paediatrics and Child Health, College of Health Sciences, Makerere University, Kampala, Uganda

<sup>4</sup> Department of Pediatrics and Child Health, Makerere University College of Health Sciences, Kampala, Uganda

<sup>5</sup> Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA

<sup>6</sup> Department of Epidemiology and Biostatistics, Makerere University College of Health Sciences, Kampala, Uganda

<sup>7</sup> Department of Pediatrics, Division of Hematology, Oncology and Stem Cell Transplantation, Columbia University Irving Medical Center, New York, NY

<sup>8</sup> Department of Psychiatry, Makerere University College of Health Sciences, Kampala, Uganda

**Introduction:** Cerebrovascular injury can lead to neurocognitive impairment in children with sickle cell anemia (SCA). The prospective impact of hydroxyurea therapy on neurocognitive function has not been previously reported in a large sample of children with SCA in sub-Saharan Africa. We assessed the impact of hydroxyurea therapy at the trial's 18-month midpoint on neurocognitive function compared to baseline assessments and to non-SCA controls.

**Methods:** A sample of 267 children with SCA, ages 3 to 9 years, were randomly selected for screening and enrollment from eligible patients who attended the Mulago Hospital Sickle Cell Clinic (MHSCC). BRAIN SAFE II is an open label hydroxyurea treatment trial with escalation to maximal tolerated dose. Primary outcomes are stroke, stroke risk and neurocognitive assessment. Controls were aged 3 to 12 years and siblings/relatives of participants with SCA. Attention, cognition and executive function were assessed for all participants by age-appropriate neurocognitive testing. Control established test z-scores for each age. Baseline (month 0) SCA group z-scores were compared to the controls and to the SCA sample at trial month 18.

**Results:** At trial baseline, SCA trial participants (n=267) were younger than the control group (mean age 5.1±1.7 vs. 7.1±3.9 years, p<0.001), had lower weight-for-age (p=0.03) and had similar socio-economic score and caregiver age and educational attainment. Participants had lower z-scores in attention (p<0.001) and neurocognitive ability (p<0.001), and in executive function (p=0.001) in a total of 15 of 17 subtests. After 18 months of hydroxyurea therapy (mean dose 25.4mg/kg) for all active SCA participants (95.1%) (n=254), significant improvements in z-scores were seen at 18 months in attention (p<0.001), all 4 subtests for cognitive ability (p<0.001) and in 3 of 6 subtests of executive function (p=0.003 to <0.001).

**Conclusion:** After 18 months of hydroxyurea therapy reaching MTD dosing, children showed significant improvements in attention and cognition, with more modest improvements in executive function. Their scores moved closer to those from non-SCA controls in most subtests. These findings suggest that hydroxyurea therapy may play an important role in enhancing overall neurocognitive function in children with SCA. Trial procedures are ongoing to assess the effects from longer-term therapy.

**Disclosures Green:** AddMedica: Other: Donated study drug for an NIH-funded clinical trial.

**Table. Neurocognitive testing: Children with SCA vs. sibling/relative controls and SCA at trial month 0 vs. month 18 on Hydroxyurea.** Children with SCA (n=267) scored lower performed worse on almost all sub-tests compared to non-SCA sibs/relatives (n=110) by age-adjusted z-scores, and scored closer to controls in most domain sub-tests after 18 months of hydroxyurea therapy (escalated to maximum tolerated dose).

|                      |                                     | Baseline           |                      |              | Months 0 vs. 18    |                          |              |
|----------------------|-------------------------------------|--------------------|----------------------|--------------|--------------------|--------------------------|--------------|
|                      |                                     | SCA m.0<br>(N=267) | Controls*<br>(N=110) | p-values     | SCA m.0<br>(N=267) | SCA m.18**<br>(N=254)*** | p-values     |
| <b>TOVA</b>          | TOVA ADHD                           | 0.73 ±0.75         | 0.00 ±1.00           | <0.001       | 0.73 ±0.75         | 0.53 ±0.78               | <b>0.010</b> |
| (Attention)          | TOVA response time variability (ms) | 0.94 ±0.51         | 0.00 ±1.00           | <0.001       | 0.94 ±0.51         | 0.67 ±0.67               | <0.001       |
|                      | TOVA response time (ms)             | 0.93 ±0.52         | 0.00 ±1.00           | <0.001       | 0.93 ±0.52         | 0.66 ±0.69               | <0.001       |
|                      | TOVA commission (%)                 | 0.93 ±0.52         | 0.00 ±1.00           | <0.001       | 0.93 ±0.52         | 0.66 ±0.69               | <0.001       |
|                      | TOVA omission                       | 0.94 ±0.51         | 0.00 ±1.00           | <0.001       | 0.94 ±0.51         | 0.66 ±0.68               | <0.001       |
| <b>composite</b>     | TOVA D prime                        | -0.93 ±0.51        | 0.00 ±1.00           | <0.001       | -0.93 ±0.51        | -0.66 ±0.67              | <0.001       |
| <b>KABC-II:</b>      | KABC sequential                     | -0.67 ±0.59        | 0.00 ±1.00           | <0.001       | -0.67 ±0.59        | -0.21 ±0.60              | <0.001       |
| (Cognition)          | KABC simultaneous                   | 0.44 ±0.78         | 0.00 ±1.00           | <0.001       | 0.44 ±0.78         | 0.06 ±0.79               | <0.001       |
|                      | KABC learning                       | -0.67 ±0.61        | 0.00 ±1.00           | <0.001       | -0.67 ±0.61        | -0.22 ±0.63              | <0.001       |
|                      | KABC Planning                       | -0.66 ±0.57        | 0.00 ±1.00           | <0.001       | -0.66 ±0.57        | -0.19 ±0.59              | <0.001       |
| <b>BRIEF</b>         | Global executive composite          | 0.67 ±0.57         | 0.00 ±1.00           | <0.001       | 0.67 ±0.57         | 0.20 ±0.59               | <0.001       |
| <b>NEPSY-II</b>      | Animal Sorting                      | 0.97 ±0.62         | 0.00 ±1.00           | <0.001       | 0.97 ±0.62         | 0.76 ±0.76               | 0.051        |
| (Executive Function) | Auditory Attention and Response Set | -1.09 ±0.32        | 0.00 ±1.00           | <0.001       | -1.09 ±0.32        | -0.83 ±0.61              | <0.001       |
|                      | Clocks                              | -1.05 ±0.46        | 0.00 ±1.00           | <0.001       | -1.05 ±0.46        | -0.82 ±0.67              | <b>0.006</b> |
|                      | Design Fluency                      | -0.47 ±0.92        | 0.00 ±1.00           | <b>0.001</b> | -0.47 ±0.92        | -0.34 ±0.92              | 0.200        |
|                      | Inhibition                          | 0.80 ±0.69         | 0.00 ±1.00           | <0.001       | 0.80 ±0.69         | 0.57 ±0.82               | <b>0.003</b> |
|                      | Statue                              | -0.05 ±1.06        | 0.00 ±1.00           | 0.77         | -0.05 ±1.06        | 0.15 ±1.04               | 0.097        |
| <b>ECTV</b>          | Attention                           | 0.06 ± 1.11        | 0.00 ±1.00           | 0.79         | 0.06 ± 1.11        | 1.03 ±0.15               | <0.001       |

TOVA: Test of Variables of Attention KABC-II: Kaufman Assessment Battery for Children, 2<sup>nd</sup> edition  
 BRIEF: Behavior Rating Inventory of Executive function for preschoolers and school-aged children (parent questionnaire)  
 NEPSY-II – Neuropsychology, 2<sup>nd</sup> edition ECTV: Early Childhood Vigilance Test  
 \*Controls were defined as having z-scores of 0.0±1.0 for each subtest. \*\*Mean hydroxyurea dose at trial month 18: 25.4mg/kg  
 \*\*\*Active participants

**Figure 1**

<https://doi.org/10.1182/blood-2023-190687>