SUMMARY OF RESULTS

Randomized Clinical Trial of Hydroxyurea With or Without Losartan in Children With Homozygous Sickle Cell Disease and Early Kidney Abnormalities

1. Participant Flow

Of 365 children screened, 187 (51.2%) had at least one marker of early kidney involvement. Persistent abnormalities were confirmed in 99 children after repeat assessment. Five children were excluded, and 94 were randomized to hydroxyurea (HU) plus losartan (n=48) or HU alone (n=46).

At baseline, 67 participants (71.3%) had glomerular hyperfiltration, 50 (53.2%) had persistent albuminuria, and 23 (24.5%) had both abnormalities.

Participant flow:

- Children screened: 365
- Children with at least one early kidney marker: 187 (51.2%)
- Persistent abnormalities after repeat assessment: 99
- Excluded: 5
- Randomized: 94
- HU + losartan: 48
- HU alone: 46

2. Baseline Characteristics

Baseline demographic, clinical, hematologic, biochemical, inflammatory, and renal characteristics were comparable between the two treatment groups.

The median age was 9 years (IQR, 6–12), 52.1% of participants were male, the median eGFR was 159.0 mL/min/1.73 m² (IQR, 123.9–181.4), and the median ACR was 33.9 mg/g (IQR, 10.1–77.4).

Characteristic	All patients (n=94)	HU + losartan (n=48)	HU alone (n=46)
Age, median (IQR), years	9.0 (6.0–12.0)	9.0 (7.0–12.0)	9.0 (5.8–13.0)
Male, n (%)	49 (52.1)	27 (56.3)	22 (47.8)
eGFR, median (IQR), mL/min/1.73 m²	159.0 (123.9–181.4)	160.0 (146.0–181.0)	155.0 (118.0–180.0)
Hyperfiltration, n (%)	67 (71.3)	37 (77.1)	30 (65.2)
ACR, median (IQR), mg/g	33.9 (10.1–77.4)	35.6 (12.2–79.5)	32.4 (7.8–68.8)
Hemoglobin, mean ± SD, g/dL	7.0 ± 1.1	6.8 ± 1.3	7.2 ± 0.8
HbF ≥15%, n (%)	2 (2.1)	1 (2.1)	1 (2.2)
≥3 vaso-occlusive crises, n (%)	39 (41.5)	21 (43.8)	18 (39.1)
CRP >6 mg/L, n (%)	44 (46.8)	21 (43.8)	23 (50.0)

Data are presented as mean ± standard deviation, median (interquartile range), or absolute and relative frequencies.

3. Adverse Events

Adverse events were uncommon and generally mild. In the hydroxyurea-plus-losartan group, 6/48 participants (12.5%) experienced at least one adverse event, including dizziness in 3 (6.3%) and fatigue in 3 (6.3%). In the hydroxyurea-alone group, 3/46 participants (6.5%) experienced fatigue.

No hypotension, dehydration, palpitations, edema, hyperkalemia >5.5 mEq/L, significant hematological toxicity, serious adverse events, or treatment-related deaths were reported in either group.

Adverse event	HU + losartan (n=48)	HU alone (n=46)
Dizziness	3 (6.3%)	0 (0%)
Fatigue	3 (6.3%)	3 (6.5%)
Hypotension	0	0
Dehydration	0	0
Palpitations	0	0
Edema	0	0
Hyperkalemia >5.5 mEq/L	0	0
Significant hematological toxicity	0	0
Serious adverse event	0	0
Treatment-related death	0	0
At least one adverse event	**6 (12.5%)**	**3 (6.5%)**

4. Outcome Measures

Primary Outcome

The primary endpoint was defined as normalization or a ≥50% reduction in at least one early kidney damage marker.

The primary endpoint was achieved in **83.3%** of participants receiving HU plus losartan compared with **63.0%** of those receiving HU alone.

Renal Outcomes

Repeated-measures analysis showed a significant effect of time on renal parameters in both groups ($P<0.001$).

Median ACR decreased progressively in both groups. In the HU-plus-losartan group, median ACR decreased from 35.6 mg/g at baseline to 21.0 mg/g at month 3, 9.5 mg/g at month 6, and 4.0 mg/g at month 9 ($P<0.001$). In the HU-alone group, median ACR decreased from 32.4 mg/g at baseline to 17.0 mg/g at month 3, 11.0 mg/g at month 6, and 9.0 mg/g at month 9 ($P<0.001$).

Glomerular hyperfiltration progressively resolved in both groups. In the HU-plus-losartan group, hyperfiltration decreased from 77.1% at baseline to 18.6% at month 3 and 0% at month 6. In the HU-alone group, it decreased from 65.2% at baseline to 30.4% at month 3 and 0% at month 6. No participant had hyperfiltration at month 9 in either group.

Persistent kidney markers decreased from 100% at baseline to 35.4%, 22.9%, and 16.7% at months 3, 6, and 9, respectively, in the HU-plus-losartan group. In the HU-alone group, the corresponding proportions were 100%, 47.8%, 57.3%, and 37.0%. Between-group differences were significant at month 6 (P=0.002) and borderline at month 9 (P=0.050).

Outcome	HU + losartan	HU alone
ACR at baseline, median (IQR), mg/g	35.6 (12.2–79.5)	32.4 (7.8–68.8)
ACR at month 9, median (IQR), mg/g	4.0 (2.0–10.0)	9.0 (3.0–28.3)
Hyperfiltration at baseline, n (%)	37 (77.1%)	30 (65.2%)
Hyperfiltration at month 6, n (%)	0 (0%)	0 (0%)
Hyperfiltration at month 9, n (%)	0 (0%)	0 (0%)
Albuminuria at baseline, n (%)	25 (52.1%)	25 (53.4%)
Albuminuria at month 6, n (%)	0 (0%)	3 (6.5%)
Albuminuria at month 9, n (%)	0 (0%)	0 (0%)
Persistent kidney markers at month 9	16.7%	37.0%
Primary endpoint achieved	**83.3%**	**63.0%**

Other Outcome Measures

Both treatment strategies were associated with progressive hematologic and biochemical improvement. HbF increased significantly in both groups, while LDH, indirect bilirubin, and reticulocyte counts decreased during follow-up. Platelet and inflammatory markers also generally decreased. Vaso-occlusive and hematologic crises decreased substantially during follow-up.

5. Factors Associated With Persistent Kidney Damage

At the end of follow-up, persistent kidney damage was independently associated with older age, male sex, HbF <15%, CRP ≥6 mg/L, and hydroxyurea monotherapy.

In multivariable analysis, the adjusted risk estimates were:

- Age 12–17 years: RR 1.91 (95% CI, 1.60–2.29; P<0.001)
- Age >17 years: RR 2.19 (95% CI, 1.62–3.88; P<0.001)
- Male sex: RR 2.03 (95% CI, 1.89–3.20; P=0.043)
- HbF <15%: RR 2.38 (95% CI, 1.89–3.21; P=0.033)
- CRP ≥6 mg/L: RR 3.04 (95% CI, 1.89–4.22; P<0.001)
- HU monotherapy: RR 2.81 (95% CI, 1.88–3.32; P=0.038)

6. Summary of Main Findings

Both treatment strategies were associated with improvement in early renal abnormalities and hematologic parameters during follow-up. The combination of hydroxyurea and losartan was associated with a greater reduction in albuminuria and a lower proportion of participants with persistent kidney markers at the end of follow-up.

The primary endpoint was achieved in 83.3% of participants receiving HU plus losartan compared with 63.0% receiving HU alone. No serious adverse events or treatment-related deaths were reported in either treatment group.

Abbreviations: ACR, albumin-to-creatinine ratio; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbF, fetal hemoglobin; HU, hydroxyurea; IQR, interquartile range; LDH, lactate dehydrogenase; RR, risk ratio; SD, standard deviation.