Long-Term Efficacy and Safety of Sparsentan in Young Patients With FSGS: 240-Week Analysis of the DUET Open-Label Extension (OLE)

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TRAVERE THERAPEUTICS

RESULTS

Baseline Characteristics

- Among 26 young patients who received at least one dose of sparsentan, 23% had documented nephrotic syndrome in their medical history or at baseline and 73% had nephrotic range proteinuria at baseline, defined as UP/C ≥2.0 g/g in patients age <18 years and ≥3.5 g/g in patients age 18-21 years (**Table 1**)
- Baseline mean eGFR was 91.4 mL/min/1.73 m^2, with wide variation between patients (range: 30-212 mL/min/1.73 m^2)

Table 1. Demographics and Disease Characteristics at Baseline in Patients Age ≤21 Years

	All Sparsentan (N=26)
Age, years, mean ± SD / median (min, max)	15.0 ± 4.0 / 16.0 (8, 21)
Female, n (%)	14 (54)
Race, n (%)	
White	19 (73)
Black or African American	5 (19)
Other	2 (8)
Blood pressure, mmHg, mean ± SD	
Systolic	124.8 ± 13.3
Diastolic	78.4 ± 9.2
UP/C, g/g, mean ± SD / median (min, max)	4.9 ± 3.9 / 3.6 (1.0, 14.0)
Documented nephrotic syndrome in medical history or at baseline, n (%)	6 (23)
Nephrotic range proteinuria*, n (%)	19 (73)
eGFR, mL/min/1.73 m^2, mean ± SD / median (min, max)	91.4 ± 55.1 / 74.7 (30, 212)
Any immunosuppressive treatment for renal indications at baseline, n (%)	12 (46)
Steroids	5 (19)
CNI	9 (35)
MMF	4 (15)
ACEi or ARB use before washout, n (%)	20 (77)
≥1 diuretic or antihypertensive agent, n (%)	11 (42)
Diuretic use, n (%)	9 (3)
Additional antihypertensive treatments (not RAASi), n (%)	6 (23)
Age at FSGS diagnosis, years, mean ± SD / median (IQR)	12.2 ± 5.6 / 14.5 (8.0, 16.8)
Time from FSGS diagnosis to informed consent, years, mean ± SD / median (IQR)	3.2 ± 3.9 / 1.9 (0.8, 4.6)

UP/C measured in first morning void samples. eGFR derived using the Modified Schwartz formula for patients age <18 years and the Modification of Diet in Renal Disease formula for patients age 18-21 years.
*UP/C ≥2.0 g/g in patients aged <18 years; ≥3.5 g/g in patients aged 18-21 years.
ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; IQR, interquartile range; MMF, mycophenolate mofetil; UP/C, urine protein/creatinine ratio; RAASi, renin-angiotensin-aldosterone system inhibitors; SD, standard deviation.

Efficacy

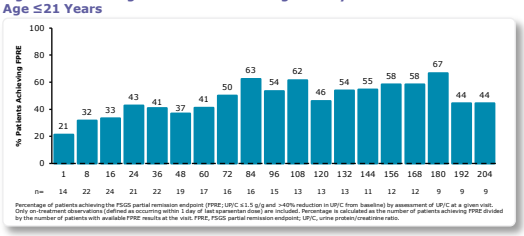
- 38% (10/26) young patients experienced at least one complete remission (CR) of proteinuria (UP/C ≤0.3 g/g) at any time; CR was achieved within 1 year of the first sparsentan dose by 7 of the 10 patients with CR
- The median (interquartile range) duration of sustained complete remission was 55.7 months (36.1, 58.5) among patients with sustained remission (n=4)
- The percentage of patients achieving the FSGS partial remission endpoint (FPRE) was 37% at 1 year, 62% at 2 years, 58% at 3 years, and 44% at 4 years (**Figure 2**)
- Young patients had a numerically lower rate of eGFR decline (based on 2-year and all-treatment eGFR slope estimates in DUET) when compared with 2-year slope estimates for patients who had a 50% proteinuria response in the FSGS Clinical Trial (FSGS-CT)[5] (**Figure 3**)
- In contrast, young patients in DUET had a numerically higher rate of eGFR decline compared with all follow-up data from patients who had a 50% proteinuria response in the FSGS-CT, which may in part be explained by the small number of patients and higher variability in eGFR slope estimates from the DUET OLE[5] (**Figure 3**)

Table 2. UP/C and Change From Baseline in UP/C Every 24 Weeks in Patients Age ≤21 Years

Study Week	n	UP/C, g/g: Median (IQR)	UP/C, g/g: Median (IQR) change from baseline	Median (IQR) % change from baseline
Baseline	26	2.9 (1.7, 5.1)	-	-
24	21	1.5 (0.6, 2.6)	-0.8 (-1.4, -0.3)	-42.1 (-72.1, -8.72)
72	16	0.9 (0.4, 2.9)	-1.1 (-2.4, -0.3)	-68.0 (-87.0, -21.6)
96	15	1.4 (0.4, 3.3)	-1.2 (-2.4, -0.5)	-57.3 (-72.6, -15.5)
120	13	1.5 (0.4, 2.3)	-1.3 (-2.6, -0.8)	-58.2 (-85.4, -25.1)
144	11	1.5 (0.1, 1.9)	-1.3 (-2.5, -0.8)	-62.6 (-91.5, -31.9)
168	12	1.2 (0.2, 2.9)	-1.3 (-1.5, -0.3)	-47.4 (-91.8, -7.3)
192	9	1.3 (0.8, 2.3)	-1.2 (-1.5, -0.4)	-54.8 (-72.9, -12.0)

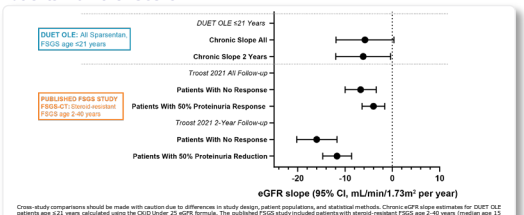
UP/C measured in first morning void samples. IQR, interquartile range; UP/C, urine protein/creatinine ratio.

Figure 2. Percentage of Patients Achieving FPRE by Visit in Patients Age ≤21 Years



Percentage of patients achieving the FSGS partial remission endpoint (FPRE; UP/C ≤1.5 g/g and >40% reduction in UP/C from baseline) by assessment of UP/C at a given visit. Only on-treatment observations (defined as occurring within 1 day of last sparsentan dose) are included. Percentage is calculated as the number of patients achieving FPRE divided by the number of patients with available FPRE results at the visit. FPRE, FSGS partial remission endpoint; UP/C, urine protein/creatinine ratio.

Figure 3. eGFR Slope Estimates (95% CI) in Patients Age ≤21 Years and in Patients From the FSGS-CT

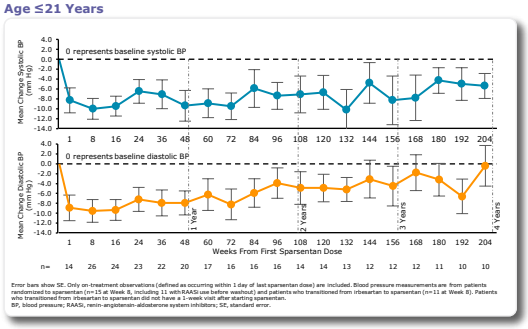


Cross-study comparisons should be made with caution due to differences in study design, patient populations, and statistical methods. Chronic eGFR slope estimates for DUET OLE patients age ≤21 years calculated using the CKiD Under 25 eGFR formula. The published FSGS study included patients with steroid-resistant FSGS age 2-<6 years (median age 15 years) with no proteinuria response to treatment and with 50% proteinuria response to treatment (all follow-up and 2-year follow up are shown, Troost 2021[5]). CKiD, Chronic Kidney Disease in Children; eGFR, estimated glomerular filtration rate; FSGS-CT, FSGS Clinical Trial; OLE, open-label extension.

Blood Pressure

- Following an early decline in blood pressure, mean systolic and diastolic blood pressure remained stable through approximately 4 years on treatment (**Figure 4**)

Figure 4. Mean Change From Baseline in Blood Pressure by Visit in Patients Age ≤21 Years



Error bars show SE. Only on-treatment observations (defined as occurring within 1 day of last sparsentan dose) are included. Blood pressure measurements are from patients randomized to sparsentan (n=15 at Week 8, including 11 with RAASi use before washout) and patients who transitioned from irbesartan to sparsentan (n=11 at Week 8). Patients who transitioned from irbesartan to sparsentan did not have a 1-week visit after starting sparsentan.
BP, blood pressure; RAASi, renin-angiotensin-aldosterone system inhibitors; SE, standard error.

Safety

- The most common treatment-related TEAEs by year of treatment among young patients are shown in **Table 3**
- There were no deaths and no kidney deaths while patients were receiving sparsentan
- One patient (4%) had an elevation ≥3× the upper limit of normal (ULN) in alanine aminotransferase; there were no such elevations in aspartate aminotransferase
- The median time to treatment discontinuation was 2.5 years (95% confidence interval, 1.0-4.9 years)
- The most common TEAE that led to discontinuation was pregnancy (n=2, **Table 4**)

Table 3. Most Common Treatment-Related TEAEs by Year and Cases Per 100 Patient-Years for Total Study Duration in Patients Age ≤21 Years

	n (%) Within Each Year				Total Study Duration Cases Per 100 Patient-Years (Cases/100 Patient Years)
	Year 0 to <1 n=26	Year 1 to <2 n=20	Year 2 to <3 n=16	Year 3 to <4 n=12	
Hyperkalemia	0	3 (15)	2 (13)	0	10.4
Vomiting	4 (15)	0	0	1 (8)	9.1
Nausea	3 (12)	0	0	1 (8)	6.5
Blood creatinine increased	2 (8)	0	2 (13)	0	5.2
Dizziness	1 (4)	1 (5)	0	1 (8)	5.2
Headache	4 (15)	0	0	0	5.2
Abdominal pain	2 (8)	0	0	0	3.9
Anemia	2 (8)	0	0	1 (8)	3.9
Hypotension	1 (4)	0	0	1 (8)	3.9
Acute kidney injury	1 (4)	0	1 (6)	0	2.6
Glomerular filtration rate decreased	2 (8)	0	0	0	2.6
Hemoglobin decreased	2 (8)	0	0	0	2.6

Treatment-related TEAEs occurring in ≥2 patients are reported.
TEAEs, treatment-emergent adverse events.

Table 4. Reasons for Study Discontinuation by Year in Patients Age ≤21 Years

	n (%)*			
	Year 0 to <1 n=26	Year 1 to <2 n=20	Year 2 to <3 n=16	Year 3 to <4 n=12
Ongoing	18 (69)	16 (62)	12 (46)	10 (38)
Discontinued	8 (31)	2 (8)	4 (15)	2 (8)
Adverse event	4 (15)	0	1 (4)	0
Lost to follow-up	1 (4)	0	0	0
Physician decision	1 (4)	1 (4)	2 (8)	0
Pregnancy	1 (4)	0	0	1 (4)
Withdrawal by subject	1 (4)	1 (4)	0	1 (4)
Noncompliance with study drug	0	0	1 (4)	0

TEAEs while on sparsentan led to study discontinuation in 9 patients over the total study duration. The TEAE pregnancy led to discontinuation in 2 patients and all other TEAEs that led to discontinuation occurred in 1 patient over the total study duration (Year 0 to <1: abdominal pain, anemia, eructation, face edema, glomerular filtration decreased, pain; Year 2 to <3: blood creatinine increased; Year 4 to <5: acute kidney injury, end stage renal disease).
*Percentages calculated using the total number of patients (n=26) as denominator.
TEAEs, treatment-emergent adverse events.

Concomitant Immunosuppressive Therapy

- The percentage of young patients receiving immunosuppressive therapy remained stable over time, whereas the proportion receiving steroids declined over time (**Table 5**)

Table 5. Concomitant Immunosuppressive Therapy Medications in Patients Age ≤21 Years

	n (%) Within Each Year			
	Year 0 to <1 n=26	Year 1 to <2 n=20	Year 2 to <3 n=16	Year 3 to <4 n=12
Immunosuppressant treatment for renal indications while on sparsentan	13 (50)	9 (45)	6 (38)	6 (50)
Steroids	5 (19)	2 (10)	1 (6)	1 (8)
Calcineurin inhibitor	10 (38)	8 (40)	6 (38)	6 (50)
Mycophenolate mofetil	4 (15)	2 (10)	1 (6)	1 (8)
Rituximab	0	0	1 (6)	1 (8)

CONCLUSIONS

- Almost half of young patients with FSGS who continued sparsentan in the OLE remained in FPRE over ~4 years
- No new or unexpected treatment-related TEAEs were observed with long-term sparsentan treatment in young patients with FSGS
- Sparsentan appeared safe and well-tolerated over 240 weeks of treatment in young patients with FSGS

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DISCLOSURES

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BACKGROUND

- There is a high unmet need for treatments that reduce proteinuria and delay the decline in kidney function in pediatric patients with focal segmental glomerulosclerosis (FSGS)
- Sparsentan is a novel, non-immunosuppressive, single molecule, dual endothelin angiotensin receptor antagonist (DEARA) with high selectivity for the endothelin type A receptor (ET_AR) and the angiotensin II subtype 1 receptor (AT_1R)[1]
- Sparsentan significantly reduced proteinuria versus the active control irbesartan in the 8-week double-blind period of the phase 2 DUET trial in patients with FSGS aged 8-75 years[2]
- A post-hoc analysis of the DUET open-label extension (OLE) in patients aged 8-75 years who continued sparsentan treatment through 240 weeks supported the long-term nephroprotective potential and safety of sparsentan in FSGS[3]

Objective

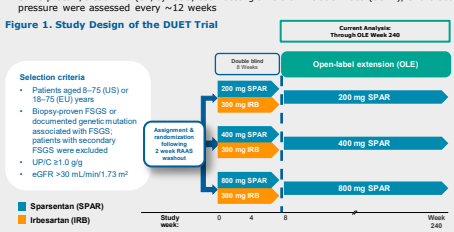
- Report the on-treatment long-term efficacy and safety of sparsentan in young patients (age ≤21 years) based on a 240-week post-hoc analysis of the DUET OLE

METHODS

Study Design

- Patients were randomly assigned to receive sparsentan or irbesartan in the 8-week double-blind period after a 2-week renin-angiotensin-aldosterone system inhibitor washout (**Figure 1**)
- All patients who completed the double-blind period, including those randomized to irbesartan, were eligible to receive sparsentan in the OLE
- Urine protein/creatinine (UP/C) ratio, estimated glomerular filtration rate (eGFR), and blood pressure were assessed every ~12 weeks

Figure 1. Study Design of the DUET Trial



UP/C, urine protein/creatinine; eGFR, estimated glomerular filtration rate; IRB, irbesartan; RAAS, renin-angiotensin-aldosterone system; SPAR, sparsentan.

Eligibility Criteria

- Key eligibility criteria were: age 8-75 years (US) or 18-75 years (EU), biopsy-proven FSGS or a disease-causing genetic mutation associated with FSGS, UP/C ratio ≥1 g/g, and eGFR >30 mL/min/1.73 m^2

Analysis

- This post-hoc analysis of the OLE included patients age ≤21 years at baseline who received ≥1 dose of sparsentan (data cutoff: February 5, 2021)
- Outcomes were analyzed from the time of first sparsentan dose, starting in the double-blind period (ie, Day 1 for patients randomized to sparsentan) or in the OLE (ie, Week 8 for patients randomized to irbesartan who transitioned to sparsentan in the OLE), through 240 weeks (4.6 years)
- Outcomes assessed:
  - Percentage of patients achieving complete remission of proteinuria (UP/C ≤0.3 g/g) at any time during the study
  - UP/C at each visit and change from baseline in UP/C at each visit
  - Percentage of patients achieving the FSGS partial remission endpoint[4] (FPRE; UP/C ≤1.5 g/g and >40% reduction in UP/C from baseline) at each visit
  - eGFR
  - Blood pressure
  - Treatment-related treatment-emergent adverse events (TEAEs)

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