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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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RESULTS

Baseline Characteristics

- Among 26 young patients who received at least one dose of sparsentan, 23.1% had documented nephrotic syndrome in their medical history or at baseline and 73.1% 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 m², with wide variation between patients (range: 30-212 mL/min/1.73 m²)

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 (53.8)
Race, n (%)	
White	19 (73.1)
Black or African American	5 (19.2)
Other	2 (7.7)
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 (23.1)
Nephrotic range proteinuria*, n (%)	19 (73.1)
eGFR, mL/min/1.73 m², mean ± SD / median (min, max)	91.4 ± 55.1 / 74.7 (30, 212)
Any immunosuppressive treatment for renal indications at baseline, n (%)	12 (46.2)
Steroids	5 (19.2)
CNI	9 (34.6)
MMF	4 (15.4)
ACEi or ARB use before washout, n (%)	20 (76.9)
≥1 diuretic or antihypertensive agent, n (%)	11 (42.3)
Diuretic use, n (%)	9 (34.6)
Additional antihypertensive treatments (not RAASi), n (%)	6 (23.1)
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.
*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

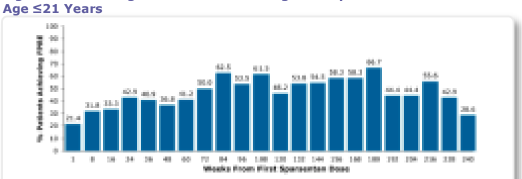
- 38.5% (10/26) young patients experienced at least one complete remission of proteinuria (UP/C ≤0.3 g/g) at any time
- The median (interquartile range) duration of sustained complete remission was 55.7 months (36.1, 58.5)
- The percentage of patients achieving the FPRE was 36.8% at 1 year, 61.5% at 2 years, 58.3% at 3 years, and 44.4% at 4 years (**Figure 2**)
- eGFR slope estimates for young patients who received sparsentan in the DUET OLE compared with published studies of patients with FSGS are shown in **Figure 3**

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

Study Week	n	UP/C, g/g Mean (SE)	Mean (SE) change from baseline	Mean (SE) % change from baseline
Baseline	26			
24	21			-35.9 (11.2)
72	16			-38.1 (19.9)
96	15			-41.2 (12.7)
120	13			-22.8 (26.9)
144	11			-46.7 (21.0)
168	12			-1.5 (43.5)
192	9			-25.6 (28.2)
216	9			-40.8 (21.7)
240	7			-3.9 (37.6)

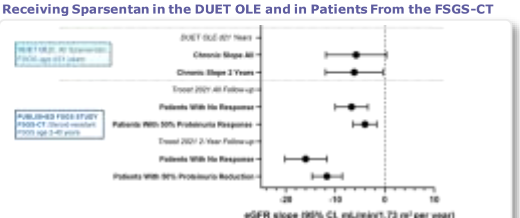
UP/C measured in first morning void samples. SE, standard error; UP/C, urine protein/creatinine ratio.

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 Receiving Sparsentan in the DUET OLE and in Patients From the FSGS-CT

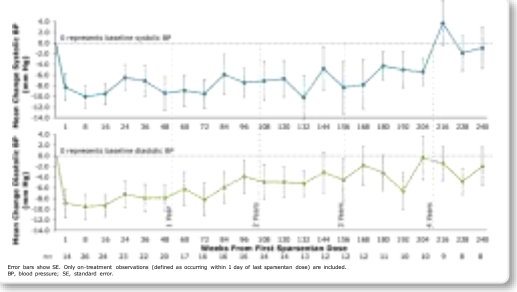


Cross-study comparisons should be made with caution due to differences in study design, patient populations, and statistical methods. Chronic eGFR slope estimates for DUET OLE patients age ≤21 years calculated using the CKiD Under 25 eGFR formula. The published FSGS study included patients with steroid-resistant FSGS age 2-40 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.
BP, blood pressure; 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 (4.5%) 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	Year 4 to <5 n=10	
Hyperkalemia	0	3 (15.0)	2 (12.5)	0	1 (10.0)	10.4
Vomiting	4 (15.4)	0	0	1 (8.3)	0	9.1
Nausea	3 (11.5)	0	0	1 (8.3)	0	6.5
Blood creatinine increased	2 (7.7)	0	2 (12.5)	0	0	5.2
Dizziness	1 (3.8)	1 (5.0)	0	1 (8.3)	0	5.2
Headache	4 (15.4)	0	0	0	0	5.2
Abdominal pain	2 (7.7)	0	0	0	0	3.9
Anemia	2 (7.7)	0	0	1 (8.3)	0	3.9
Hypotension	1 (3.8)	0		1 (8.3)	0	3.9
Acute kidney injury	1 (3.8)	0	1 (6.3)	0	0	2.6
Glomerular filtration rate decreased	2 (7.7)	0	0	0	0	2.6
Hemoglobin decreased	2 (7.7)	0	0	0	0	2.6

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	Year 4 to <5 n=10
Ongoing	18 (69.2)	16 (61.5)	12 (46.2)	10 (38.5)	8 (30.8)
Discontinued	8 (30.8)	2 (7.7)	4 (15.4)	2 (7.7)	2 (7.7)
Adverse event	4 (15.4)	0	1 (3.8)	0	2 (7.7)
Lost to follow-up	1 (3.8)	0	0	0	0
Physician decision	1 (3.8)	1 (3.8)	2 (7.7)	0	0
Pregnancy	1 (3.8)	0	0	1 (3.8)	0
Withdrawal by subject	1 (3.8)	1 (3.8)	0	1 (3.8)	0
Noncompliance with study drug	0	0	1 (3.8)	0	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	Year 4 to <5 n=10
Immunosuppressant treatment for renal indications while on sparsentan	13 (50.0)	9 (45.0)	6 (37.5)	6 (50.0)	5 (50.0)
Steroids	5 (19.2)	2 (10.0)	1 (6.3)	1 (8.3)	1 (10.0)
Calcineurin inhibitor	10 (38.5)	8 (40.0)	6 (37.5)	6 (50.0)	5 (50.0)
Mycophenolate mofetil	4 (15.4)	2 (10.0)	1 (6.3)	1 (8.3)	1 (10.0)
Rituximab	0	0	1 (6.3)	1 (8.3)	0

CONCLUSIONS

- Almost half of young patients 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
- Sparsentan appeared safe and well-tolerated over 240 weeks of treatment in young patients

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DISCLOSURES

KL: Received honoraria from Alexion Pharmaceuticals, Travere Therapeutics, Inc.; **AP**: Principal Investigator with Travere Therapeutics, Inc.; **TS**: Received research funding from National Institutes of Health, Travere Therapeutics, Inc., Alexion, Mallinckrodt Pharmaceuticals, and Bristol Meyers Squibb; **RK** and **EM**: Employees of and stockholders for Travere Therapeutics, Inc.; **HT**: Served as a consultant to and/or a member of a data monitoring committee for Akebia, ChemoCentryx, Goldfinch Bio, Inc., Natera, Otsuka, Travere Therapeutics, Inc., and Walden.

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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 that is a dual-acting, highly selective antagonist of both 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

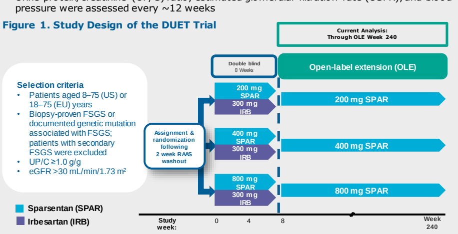
- Report the on-treatment long-term efficacy and safety of sparsentan in young patients (age ≤21 years) based on a 240-week post-hoc analysis of the DUET OLE

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



Current Analysis: Through OLE Week 240
Double blind 8 Weeks
Open-label extension (OLE)
Selection criteria
Patients aged 8–75 (US) or 18–75 (EU) years
Biopsy-proven FSGS or documented genetic mutation associated with FSGS; patients with secondary FSGS were excluded
UP/C ≥1.0 g/g
eGFR >30 mL/min/1.73 m²
Assignment & randomization following 2 week RAAS washout
200 mg SPAR
300 mg IRB
400 mg SPAR
300 mg IRB
800 mg SPAR
300 mg IRB
200 mg SPAR
400 mg SPAR
800 mg SPAR
Sparsentan (SPAR)
Irbesartan (IRB)
Study week:
0
4
8
Week 240

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 m²

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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