Sparsentan vs Irbesartan in Patients With Focal Segmental Glomerulosclerosis (FSGS): Results From the Phase 3 DUPLEX Trial

Michelle N. Rheault,1* Howard Trachtman,2* Ulysses Diva,3 and Radko Komers3 on behalf of the DUPRO steering committee and DUPLEX investigators

1Division of Pediatric Nephrology, University of Minnesota Medical School, Minneapolis, MN, USA; 2Division of Nephrology, Department of Pediatrics, University of Michigan, Ann Arbor, MI, USA; 3Travere Therapeutics, Inc., San Diego, CA, USA. *Authors contributed equally.

Presented at the American Society of Nephrology Kidney Week Annual Meeting; November 1–5, 2023; Philadelphia, PA

Contact information: Michelle N. Rheault, rheau002@umn.edu
• **MNR** has served as a site PI for clinical trials funded by Akebia, Chinook, Reata, River 3 Renal, Sanofi, and Travere Therapeutics, Inc.; and as a consultant for ENYO Pharma, Walden Biosciences, and Visterra.

• **HT** has received consulting fees from Aclipse, Boehringer Ingelheim, Maze Therapeutics, Natera, Otsuka, PhaseV, Travere Therapeutics, Inc., and Walden; received speaking honoraria from National Kidney Foundation; participated on data safety monitoring or advisory boards for ChemoCentryx, Otsuka, and Travere Therapeutics, Inc.

• **UD** and **RK** are employees of Travere Therapeutics, Inc. and may have an equity or other financial interest in Travere Therapeutics, Inc.
Background

• There are no approved therapies for FSGS, highlighting an unmet need for safe and effective treatments that lower proteinuria and reduce the risk of kidney failure\textsuperscript{1-3}

• Sparsentan is an orally active dual endothelin angiotensin receptor antagonist (DEARA)\textsuperscript{1,4-5} that reduced proteinuria in patients with FSGS in a phase 2 trial\textsuperscript{6}

Dual ET\textsubscript{A} and AT\textsubscript{1} receptor antagonism has anti-inflammatory, antiproliferative, and antifibrotic actions of therapeutic potential in addition to hemodynamic benefits\textsuperscript{1,4,7-9}

Phase 3 DUPLEX Study

• **Objective:** Evaluate the efficacy and safety of sparsentan vs the active control irbesartan in patients with FSGS

• **Trial Design:** Phase 3, double-blind, active-controlled global trial (NCT03493685) in patients with biopsy-proven FSGS or genetic FSGS
## Phase 3 DUPLEX Study

- **Objective:** Evaluate the efficacy and safety of sparsentan vs the active control irbesartan in patients with FSGS.
- **Trial Design:** Phase 3, double-blind, active-controlled global trial (NCT03493685) in patients with biopsy-proven FSGS or genetic FSGS.

### Methods

**Washout period**

- **2 weeks**

**Double-blind treatment**

- **108 weeks**

**Resume SOC, including RAASi**

- **4 weeks postcessation of randomized treatment**

### Screening

- **Ages 8-75 years**
- **FSGS (excluding secondary causes)**
- **UPCR ≥1.5 g/g**
- **eGFR ≥30 mL/min/1.73 m²**

### No RAASI

- **Discontinue RAASI**
- **Baseline**

### Sparsentan

- **400 mg/day** → **800 mg/day at week 2**

### Irbesartan

- **150 mg/day** → **300 mg/day at week 2**

### Week 36

- Prespecified interim analysis

### Week 108

- End of double-blind treatment

### Week 112

- Last double-blind assessment
Phase 3 DUPLEX Study

• **Objective:** Evaluate the efficacy and safety of sparsentan vs the active control irbesartan in patients with FSGS

• **Trial Design:** Phase 3, double-blind, active-controlled global trial (NCT03493685) in patients with biopsy-proven FSGS or genetic FSGS

### Screening

- Ages 8-75 years
- FSGS (excluding secondary causes)
- UPCR ≥1.5 g/g
- eGFR ≥30 mL/min/1.73 m²

### Washout period

- 2 weeks

### Double-blind treatment

- 108 weeks

### Resume SOC, including RAASi

### Surrogate Efficacy Endpoint

(36-Week Interim Analysis)

- Proportion of patients achieving FPRE at week 36 (UPCR ≤1.5 g/g and ≥40% reduction from baseline)

### Primary Endpoint

- eGFR chronic slope (week 6 to 108)
- eGFR total slope (day 1 to week 108)
RESULTS

Patient Disposition

- 724 patients screened for eligibility
- 371 randomized

**Sparsentan**
- 184 randomized to sparsentan
- 91% titrated to target dose of 800 mg/day
- 129 (70%) completed double-blind treatment
- 168 (91%) completed study double-blind period
- 55 discontinued treatment
  - 24 AE
  - 14 patient decision
  - 9 physician decision
  - 8 other reason
- 16 discontinued study double-blind period

**Irbesartan**
- 187 randomized to irbesartan
- 90% titrated to target dose of 300 mg/day
- 136 (73%) completed double-blind treatment
- 171 (91%) completed study double-blind period
- 51 discontinued treatment
  - 19 AE
  - 18 patient decision
  - 6 physician decision
  - 8 other reason
- 16 discontinued study double-blind period

NCT03493685
Baseline Demographics and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sparsentan n=184</th>
<th>Irbesartan n=187</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD), years</strong></td>
<td>41.7 (16.5)</td>
<td>41.5 (17.3)</td>
</tr>
<tr>
<td>&lt;18 years, n (%)</td>
<td>16 (8.7)</td>
<td>19 (10.2)</td>
</tr>
<tr>
<td><strong>Male sex, n (%)</strong></td>
<td>101 (55)</td>
<td>99 (53)</td>
</tr>
<tr>
<td><strong>eGFR, mean (SD), mL/min/1.73 m²</strong></td>
<td>63.3 (28.6)</td>
<td>64.1 (31.7)</td>
</tr>
<tr>
<td><strong>UPCR, g/g</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>3.1 (2.27-4.47)</td>
<td>3.0 (2.10-4.66)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3.74 (2.32)</td>
<td>3.70 (2.70)</td>
</tr>
<tr>
<td><strong>Blood pressure, mean (SD) systolic/diastolic, mm Hg</strong></td>
<td>133.1 (14.8)/85.5 (10.6)</td>
<td>130.9 (14.6)/82.4 (10.1)</td>
</tr>
<tr>
<td><strong>FSGS-associated genetic variants, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monogenic variants in podocyte structure/function proteins</td>
<td>15 (9)</td>
<td>18 (10)</td>
</tr>
<tr>
<td>COL4A3-5 variants</td>
<td>12 (7)</td>
<td>15 (8)</td>
</tr>
<tr>
<td>High-risk APOL1 variants</td>
<td>9 (5)</td>
<td>5 (3)</td>
</tr>
<tr>
<td><strong>Prior RAASi use (stopped before washout), n (%)</strong></td>
<td>152 (83)</td>
<td>143 (76)</td>
</tr>
<tr>
<td><strong>Baseline use of immunosuppressive agents, n (%)</strong></td>
<td>50 (27)</td>
<td>46 (25)</td>
</tr>
<tr>
<td><strong>Baseline use of diuretics, n (%)</strong></td>
<td>68 (37)</td>
<td>73 (39)</td>
</tr>
</tbody>
</table>
MorePatientsAchievedtheFSGSPartialRemissionEndpoint\(^1\) (FPRE; UPCR ≤1.5 g/g and >40% Reduction From Baseline) With Sparsentan vs Irbesartan


**RESULTS**

Sparsentan resulted in a significantly higher rate of FPRE vs irbesartan after 36 weeks

<table>
<thead>
<tr>
<th>Sparsentan (n=184)</th>
<th>Irbesartan (n=187)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RR (95% CI):</strong></td>
<td><strong>Difference (95% CI):</strong></td>
</tr>
<tr>
<td>1.55 (1.10, 2.18)</td>
<td>16.0 (4.0, 28.0)</td>
</tr>
</tbody>
</table>

\( P<0.01 \)
More Patients Achieved the FSGS Partial Remission Endpoint (FPRE; UPCR ≤1.5 g/g and >40% Reduction From Baseline) With Sparsentan vs Irbesartan

**RESULTS**

FPRE, FSGS partial remission endpoint; RR, relative risk.

Interim Analysis

- **Probability of Achieving FPRE, %**
  - Sparsentan: 42.0 (RR 1.55 (1.10, 2.18))
  - Irbesartan: 26.0

Final Analysis

- **Probability of Achieving FPRE, %**
  - Sparsentan: 37.5 (RR 1.60 (1.13, 2.25))
  - Irbesartan: 22.6

Difference (95% CI): 14.9 (4.10, 25.61)

Nominal P < 0.01

This effect was maintained at the 108-week final analysis.
Sparsentan Resulted in a Rapid Decline in UPCR That Was Sustained Through 108 Weeks

**LS Mean (95% CI) Change From Baseline in UPCR, %**

**Week**

<table>
<thead>
<tr>
<th>Sparsentan, n=184</th>
<th>168</th>
<th>163</th>
<th>157</th>
<th>158</th>
<th>146</th>
<th>139</th>
<th>135</th>
<th>135</th>
<th>128</th>
<th>119</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irbesartan, n=187</td>
<td>178</td>
<td>169</td>
<td>156</td>
<td>155</td>
<td>150</td>
<td>141</td>
<td>138</td>
<td>144</td>
<td>132</td>
<td>128</td>
</tr>
</tbody>
</table>

BL, baseline; GMR, geometric mean ratio.
Complete Remission of Proteinuria (CR; UPCR <0.3 g/g) was Achieved Earlier and More Frequently With Sparsentan vs Irbesartan

Patients Achieving CR at Any Time During the Double-Blind Period

RR (95% CI): 2.47 (1.37, 4.45)

Probability of Achieving CR, %

Sparsentan

Irbesartan

No. at risk

Week

Probability of Achieving CR

Sparsentan

Irbesartan

RR, relative risk.
eGFR Endpoints Over the Double-Blind Period: Primary Endpoint

Annual eGFR chronic slope (week 6 to 108): Sparsentan (n=184) -4.8, Irbesartan (n=187) -5.7
Annual eGFR total slope (day 1 to week 108): Sparsentan (n=184) -5.4, Irbesartan (n=187) -5.7

Difference (95% CI): Sparsentan - Irbesartan 0.9 (-1.27, 3.04) 0.3 (-1.74, 2.41)
**RESULTS**

**eGFR Endpoints Over the Double-Blind Period**

**Annual eGFR**

- **chronic slope** (week 6 to 108)
  - Sparsentan (n=184): -4.8 mL/min/1.73 m²/year
  - Irbesartan (n=187): -5.7 mL/min/1.73 m²/year
  - Difference (95% CI): 0.9 (-1.27, 3.04)

- **total slope** (day 1 to week 108)
  - Sparsentan (n=184): -5.4 mL/min/1.73 m²/year
  - Irbesartan (n=187): -5.7 mL/min/1.73 m²/year
  - Difference (95% CI): 0.3 (-1.74, 2.41)

**Change in eGFR from baseline to week 112**

- Sparsentan (n=129): -10.4 mL/min/1.73 m²
  - Difference (95% CI): 1.8 (-1.39, 4.93)

- Irbesartan (n=136): -12.1 mL/min/1.73 m²

Patients who completed double-blind treatment:
- Sparsentan (n=184)
- Irbesartan (n=187)
**Treatment Effect on eGFR Slope Sensitivity Analyses**

- eGFR chronic slope was lower with sparsentan vs irbesartan when measurements after initiation or intensification of immunosuppressive treatments were excluded
  - 16.3% of patients in the sparsentan group and 16.0% in the irbesartan group required initiation or intensification of immunosuppressive treatments
- Other sensitivity analyses were consistent with the main analysis

<table>
<thead>
<tr>
<th></th>
<th>Sparsentan, n</th>
<th>Irbesartan, n</th>
<th>Annual eGFR chronic slope</th>
<th>Annual eGFR total slope</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference (95% CI) for sparsentan vs irbesartan, mL/min/1.73 m²</td>
<td>Difference (95% CI) for sparsentan vs irbesartan mL/min/1.73 m²</td>
</tr>
<tr>
<td>With multiple imputation</td>
<td>184</td>
<td>187</td>
<td>1.1 (−0.88, 2.99)</td>
<td>0.6 (−1.25, 2.53)</td>
</tr>
<tr>
<td>Excluding data after initiation or intensification of immunosuppressive treatment</td>
<td>184</td>
<td>187</td>
<td>2.1 (0.5, 4.10)</td>
<td>1.5 (−0.40, 3.44)</td>
</tr>
<tr>
<td>Excluding patients who had major protocol deviations that might affect efficacy measurements</td>
<td>164</td>
<td>170</td>
<td>1.5 (−0.74, 3.66)</td>
<td>0.9 (−1.22, 2.99)</td>
</tr>
</tbody>
</table>
Fewer Patients Reached Composite Kidney Endpoints or End-Stage Kidney Disease With Sparsentan vs Irbesartan

RR (95% CI): 0.87 (0.60, 1.26)

RR (95% CI): 0.68 (0.43, 1.10)

RR (95% CI): 0.58 (0.31, 1.07)

RR, relative risk.
Sparsentan Was Well Tolerated With a Safety Profile Comparable to That of Irbesartan

<table>
<thead>
<tr>
<th>Patients With TEAEs, n (%)</th>
<th>Sparsentan n=184</th>
<th>Irbesartan n=187</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAEs</td>
<td>172 (93)</td>
<td>174 (93)</td>
</tr>
<tr>
<td>Serious TEAEs</td>
<td>68 (37)</td>
<td>82 (44)</td>
</tr>
</tbody>
</table>

**TEAEs of interest**

<table>
<thead>
<tr>
<th>TEAEs of interest</th>
<th>Sparsentan n=184</th>
<th>Irbesartan n=187</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid retention-associated TEAEs</td>
<td>47 (26)</td>
<td>56 (30)</td>
</tr>
<tr>
<td>Hyperkalemia-associated TEAEs</td>
<td>37 (20)</td>
<td>21 (11)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>33 (18)</td>
<td>21 (11)</td>
</tr>
<tr>
<td>Anemia-associated TEAEs</td>
<td>30 (16)</td>
<td>15 (8)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>23 (13)</td>
<td>21 (11)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>8 (4)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>ALT or AST &gt;3 × ULN</td>
<td>5 (3)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

- The most common TEAEs (≥15% in either group) included COVID-19, hyperkalemia, peripheral edema, and hypotension
After an Initial Decrease, Blood Pressure Remained Stable After 4-6 Weeks

DBP, diastolic blood pressure; SBP, systolic blood pressure.
In the largest randomized trial of FSGS to date, sparsentan achieved a sustained reduction in proteinuria, with higher rates of FPRE and CR vs irbesartan.

Although differences in eGFR slopes for the sparsentan and irbesartan groups were not statistically significant, the magnitude of the difference in eGFR chronic slope is clinically meaningful as a decrease of nearly 1 mL/min/1.73 m²/year could delay the need for renal replacement therapy.

Fewer patients reached the composite kidney endpoints or end-stage renal disease with sparsentan than irbesartan.

The safety profile of sparsentan was comparable to that of irbesartan. There were no TEAEs of heart failure or liver injury and no clinically meaningful fluid retention/edema concerns were identified.

Overall, results indicate a clinical benefit of sparsentan for proteinuria reduction in patients with FSGS.

CR, complete remission of proteinuria; FPRE, FSGS partial remission endpoint.
• This study was funded by Travere Therapeutics

• Medical writing assistance and editorial support were provided under the guidance of the authors by Jackie Highland, PhD, CMPP, of ArticulateScience, LLC, in accordance with Good Publication practice guidelines and was funded by Travere Therapeutics

• The authors thank all the patients, families, and investigators who made this study possible and persevered even during the pandemic
Sparsentan versus Irbesartan in Focal Segmental Glomerulosclerosis

Questions?