SUPPLEMENTAL MATERIAL

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METHODS

Subgroup Analyses

Prespecified analyses were performed on patient subgroups of the efficacy evaluable set population stratified by age (>18 vs ≤18 years), baseline UP/C (≥3.5 vs <3.5 g/g), sex, and baseline severity of kidney disease (eGFR: >90, >60–90, >45–60, and 30–45 mL/min/1.73m^2). Analyses of subgroups based on race and blood pressure were also performed. The treatment group geometric least squares mean percent change from baseline in UP/C was calculated for both treatment groups within each patient subgroup. Analysis of covariance models for change in natural log UP/C included baseline UP/C as a covariate and effects for treatment, cohort, prognostic factor, and treatment by prognostic factor interaction. Descriptive statistics and 95% confidence intervals were calculated for each subgroup.

RESULTS

Supplemental Table 1. Reduction in UP/C From Baseline to Week 8 by Dose Group (Efficacy Evaluable Set)

	UP/C Ratio, Median (Range) Week 0		UP/C Ratio, Median (Range) Week 8		% Reduction From Baseline (95% CI)[a]		
Sparsentan Dose Cohort	**Irbesartan (n=32)**	**Sparsentan (n=64)**	**Irbesartan (n=32)**	**Sparsentan (n=64)**	**Irbesartan (n=32)**	**Sparsentan (n=64)**	***P* Value**
All doses	3.27 (0.88, 10.73) [n=32]	3.62 (0.43, 18.66) [n=64]	2.41 (0.43, 10.19) [n=32]	1.98 (0.12, 14.47) [n=64]	–18.5 (–34.6, 1.7) [n=32]	–44.8 (–52.7, –35.7) [n=64]	0.006
400 and 800 mg	2.97 (0.88, 10.73) [n=25]	3.53 (0.43, 18.66) [n=51]	2.39 (0.43, 10.19) [n=25]	1.90 (0.12, 14.47) [n=51]	–19.0 (–38.0, 5.9) [n=25]	–47.4 (–56.3, –36.9) [n=51]	0.011
200 mg	4.86 (0.98, 8.03) [n=7]	3.71 (1.50, 10.15) [n=13]	3.64 (1.45, 6.69) [n=7]	2.06 (0.59, 14.38) [n=13]	–15.0 (–41.8, 24.2) [n=7]	–33.1 (–49.3, –11.6) [n=13]	0.298
400 mg	2.85 (1.10, 10.73) [n=17]	3.71 (1.25, 18.66) [n=21]	2.38 (0.43, 10.19) [n=17]	1.73 (0.28, 12.34) [n=21]	–28.1 (–47.5, –1.6) [n=17]	–52.7 (–64.3, –37.2) [n=21]	0.056
800 mg	3.30 (0.88, 9.76) [n=8]	3.23 (0.43, 14.68) [n=30]	3.02 (1.11, 8.37) [n=8]	2.09 (0.12, 14.47) [n=30]	–9.3 (–45.3, 50.3) [n=8]	–41.3 (–54.4, –24.4) [n=30]	0.127

[a]Geometric least squares mean percent change from baseline.

P values from analysis of covariance.

Abbreviations: CI, confidence interval;UP/C, urinary protein-to-creatinine ratio.

Supplemental Table 2. MMRM Analysis of UP/C at Baseline and Week 8, All Doses (Full Analysis Set)

UP/C Ratio, Median (Range) Week 0		UP/C Ratio, Median (Range) Week 8		Comparison of the Baseline (Week 0) Adjusted Week 8 UP/C Values Between Sparsentan and Irbesartan (95% CI)[a]	
Irbesartan (n=36)	**Sparsentan (n=73)**	**Irbesartan (n=36)**	**Sparsentan (n=73)**	**Sparsentan (n=73) vs Irbesartan (n=36)**	***P* Value**
3.12 (0.88, 10.73) [n=36]	3.61 (0.43, 18.66) [n=72]	2.41 (0.43, 10.19) [n=32]	1.94 (0.12, 14.47) [n=66]	0.69 (0.52, 0.91)	0.010

[a]A mixed model repeated measures (MMRM) analysis using restricted maximum likelihood (REML) with the natural log(UP/C) at Week 0 and Week 8 as the dependent variable, treatment, cohort, visit, and treatment-by-visit interaction as fixed effects, and subject as a random effect was conducted in this analysis. The ratio for the difference from Week 8 to Week 0 is generated by exp[LSmean of natural log(UP/C) at Week 8 - LSmean of natural log(UP/C) at Week 0 for Sparsentan – LSmean of natural log(UP/C) at Week 8 - LSmean of natural log(UP/C) at Week 0 for Irbesartan]. 95% CI of ratio and *P* value are derived from the contrast of the treatments and visits within the MMRM model.

Abbreviations: CI, confidence interval; UP/C, urinary protein-to-creatinine ratio.

Supplemental Table 3. Proportion of Patients Who Achieved FPRE at Week 8 (Efficacy Evaluable Set)

	Patients, n/N (%)		
Dose Cohort	**Irbesartan (n=32)**	**Sparsentan (n=64)**	***P* Value[a]**
All doses	3/32 (9.4)	18/64 (28.1)	0.040
400 mg and 800 mg	3/25 (12.0)	16/51 (31.4)	0.092
200 mg	0/7 (0)	2/13 (15.4)	0.521
400 mg	3/17 (17.7)	8/21 (38.1)	0.282
800 mg	0/8 (0)	8/30 (26.7)	0.164

[a]Discrete outcomes were compared using a Fisher exact test.

Abbreviation: FPRE, focal segmental glomerular sclerosis (FSGS) partial remission endpoint; n/N, number achieving endpoint / number assessed.

Supplemental Table 4. Changes in Select Laboratory and Safety Parameters During the Double-blind Period (Safety Evaluable Set)

	Irbesartan (n=36)		Sparsentan, All Doses (n=73)	
Parameter	**Baseline**	**Week 8**	**Baseline**	**Week 8**
Body weight, kg	82.1 (22.1)	81.6 (22.4)	81.4 (22.4)	81.1 (22.8)
Serum albumin, g/dL	3.54 (0.72)	3.61 (0.58)	3.56 (0.71)	3.6 (0.72)
Serum creatinine, mg/dL	1.22 (0.56)	1.22 (0.58)	1.19 (0.53)	1.25 (0.59)
Serum potassium, mmol/L	4.23 (0.44)	4.47 (0.36)	4.13 (0.37)	4.43 (0.43)
Hemoglobin, g/dL	12.9 (2.1)	12.7 (2.1)	13.3 (1.9)	12.3 (2.0)
Hematocrit, %	39.4 (5.9)	39.0 (5.4)	40.2 (5.6)	37.3 (6.0)
ALT, U/L	24.3 (13.9)	23.1 (10.9)	24.2 (15.1)	20.8 (12.2)
AST, U/L	26.1 (14.7)	24.5 (10.2)	23.9 (11.7)	22.1 (11.1)
NT-proBNP, pg/mL[a]	202.3 (408.3)	125.4 (116.5)	139.1 (128.9)	146.1 (285.1)

Data presented as mean (standard deviation) and analyzed using descriptive statistics.

[a]Based on the efficacy analysis set; sparsentan (n = 64) and irbesartan (n = 32).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

Supplemental Table 5. Diuretic Use During the Double-blind Period (Full Analysis Set)

	Patients, n (%)	
Diuretic	**Irbesartan (n=36)**	**Sparsentan, All Doses (n=73)**
Thiazide	6 (16.7)	5 (6.8)
Hydrochlorothiazide	4 (11.1)	3 (4.1)
Chlorthalidone	0	1 (1.4)
Metolazone	2 (5.6)	1 (1.4)
Loop	8 (22.2)	26 (35.6)
Furosemide	8 (22.2)	25 (34.2)
Bumetanide	0	1 (1.4)

Data analyzed using descriptive statistics.

Supplemental Table 6. Change in Diuretic Treatment During the Double-blind Period (Full Analysis Set)

	Patients, n (%)	
Diuretic	**Irbesartan (n=36)**	**Sparsentan, All Doses (n=73)**
All diuretics		
New or increased	4 (11.1)	8 (11.0)
Reduced	1 (2.8)	1 (1.4)
Thiazide[a]		
New or increased	3 (8.3)	1 (1.4)
Reduced	0 (0.0)	1 (1.4)
Furosemide[b]		
New or increased	1 (2.8)	7 (9.6)
Reduced	1 (2.8)	0 (0.0)

Data analyzed using descriptive statistics.

[a]Thiazides included hydrochlorothiazide, chlorthalidone, and metolazone.

[b]No other loop diuretics change during the double-blind period.

Supplemental Table 7. Changes in UP/C for Patient Subgroups (Efficacy Evaluable Set)

		Geometric LS Mean % Change From Baseline to Week 8 (95% CI)		
Subgroup	**Patients, n Irbesartan/ Sparsentan**	**Irbesartan (n=32)**	**Sparsentan, All Doses (n=64)**	**Interaction *P* Value**
Age				0.921
>18 y	24/52	–12.1 (–30.6, 11.5)	–40.7 (–49.3, –30.6)[a]	
≤18 y	8/12	–41.1 (–72.4, 25.5)	–62.9 (–78.2, –36.9)[a]	
Sex				0.556
Male	18/37	–20.0 (–39.5, 5.8)	–41.1 (–51.3, –28.6)[a]	
Female	14/27	–8.0 (–37.6, 35.6)	–50.1 (–61.8, –34.7)[a]	
Race				0.477
White	23/51	–21.1 (–39.6, 3.1)	–43.3 (–52.6, –32.1)[a]	
Black/African American	6/6	–26.6 (–74.8, 113.9)	–56.3 (–85.2, 29.1)	
Other	3/7	35.7 (−24.8, 144.7)	-49.7 (–62.9, –31.8)[a]	
Baseline UP/C				0.207
≥3.5 g/g	14/33	–29.3 (–46.9, –5.9)[a]	–39.7 (–50.0, –27.2)[a]	
<3.5 g/g	18/31	–10.8 (–36.4, 25.2)	–46.0 (–58.3, –30.0)[a]	
Baseline eGFR[b]				0.624
>90 mL/min/1.73m^2	6/16	–14.6 (–59.0, 78.1)	–57.7 (–72.4, –35.0)[a]	
>60–90 mL/min/1.73m^2	11/18	–42.0 (–61.1, –13.6)[a]	–37.2 (–52.7, –16.7)[a]	
>45–60 mL/min/1.73m^2	7/12	–4.0 (–45.4, 68.9)	–42.5 (–62.7, –11.3)[a]	
30–45 mL/min/1.73m^2	6/16	21.5 (–30.5, 112.4)	–39.1 (−54.8, –18.1)[a]	

Baseline BP				0.981
Hypertensive	8/27	–4.4 (–42.7, 59.6)	–46.6 (–62.0, –25.0)[a]	
Normotensive	24/37	–21.3 (–38.8, 1.1)	–48.1 (–57.5, –36.6)[a]	

Data reported as mean change (95% CI). For the interaction *P* value, an analysis of covariance model was fitted for the natural log of change from baseline in UP/C with the natural log of baseline UP/C as covariate and effects for treatment, cohort, prognostic factor, and treatment by prognostic factor interaction.

[a]*P*<0.05.

[b]n=92.

Abbreviations: BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least squares; UP/C, urine protein-to-creatinine ratio.