Efficacy and Safety of Sparsentan, a Dual Angiotensin II and Endothelin Type A Receptor Antagonist, in Patients with Focal Segmental Glomerulosclerosis: A Phase 2 Trial (DUET) **(NCT01613118)**

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on behalf of the DUET Investigators

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Disclosures

- Howard Trachtman, MD
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  - Disclosure: Consultant to Otsuka and Kaneka. Steering committee member of the abatacept trial but not a consultant to BMS.
  - Part of Publication Steering Committee, Retrophin, Inc.; No financial conflicts to disclose with Retrophin, Inc.
- Peter Nelson, MD
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  - Part of Publication Steering Committee, Retrophin, Inc.; Nephrology Advisory Board member, Retrophin, Inc.
- Radko Komers, MD, PhD
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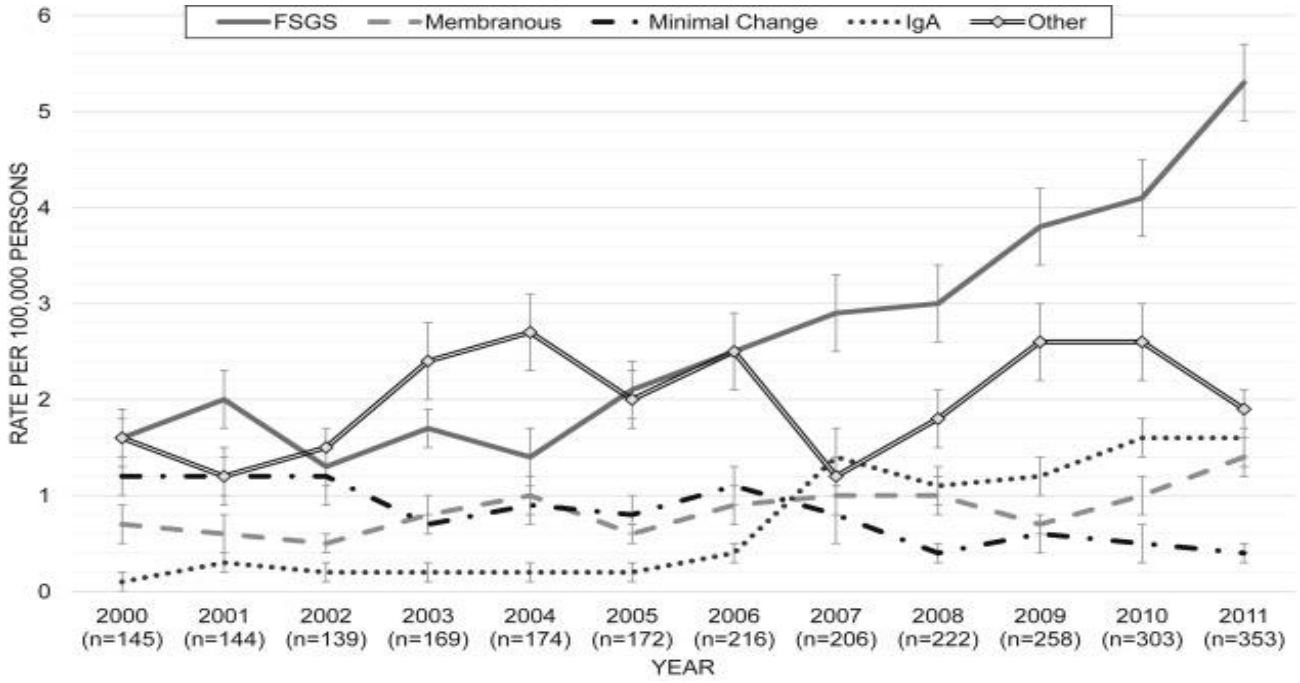
  - Disclosure: Employee of Retrophin, Inc.

Authors had full control of the content, reviewed and guided development of drafts, and provided their approval on the final presentation. Writing support for this presentation was provided by Shelly Asiala, PharmD, CMPP, from JB Ashtin and was funded by Retrophin, Inc.

Background

Primary Focal Segmental Glomerulosclerosis (FSGS)

- FSGS is a leading cause of nephrotic syndrome and end-stage renal disease (ESRD)
  - Accounts for 5% of incident adult and 12% of incident pediatric ESRD cases[1,2]



  - Approximately half of patients with nephrotic-range proteinuria will require renal replacement therapy within 5–10 years of diagnosis[3]
  - Currently no FDA-approved agents

Figure is reprinted from Sim JJ, et al. *Am J Kidney Dis.* 2016;68:533-544. doi: 10.1053/j.ajkd.2016.03.416. Open access.

1. Spino C, et al. *Front Pediatr.* 2016;4:25; 2. Saran R, et al. *Am J Kidney Dis.* 2015;66:S1-S305; 3. Korbet SM. *J Am Soc Nephrol.* 2012;23:1769-1776.

Current Standard of Care

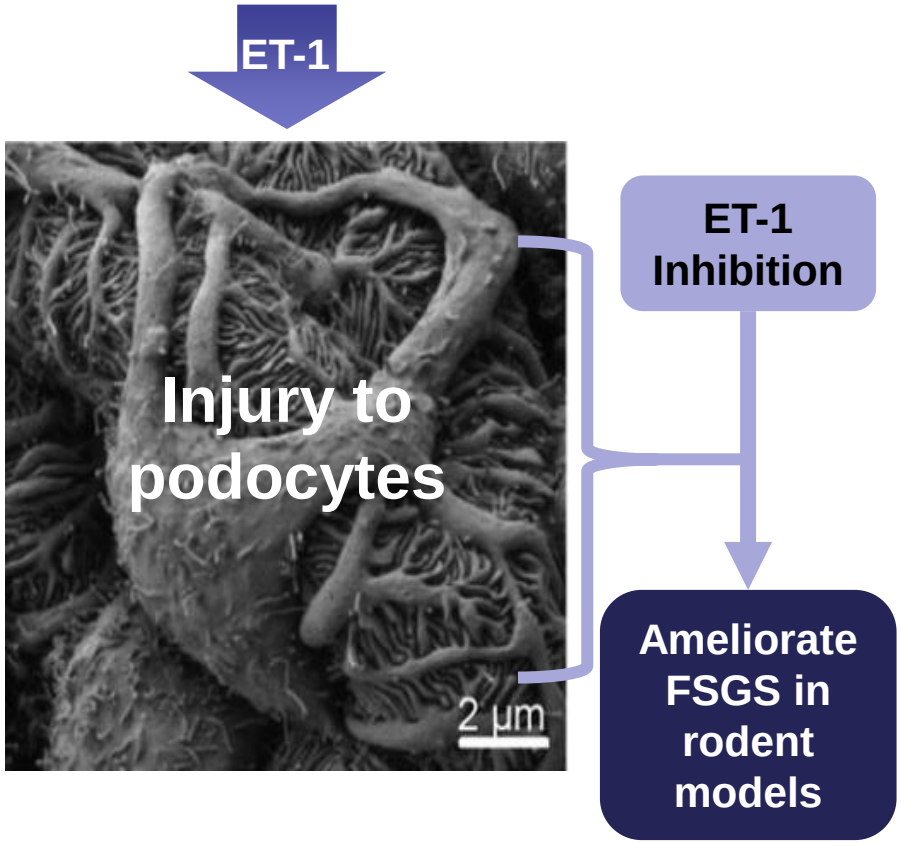
- KDIGO guidelines recommend renin-angiotensin system blockade to help reduce proteinuria[1]
- ACEIs and ARBs have demonstrated anti-proteinuric and reno-protective benefits in CKD with proteinuria
  - Have not been extensively studied in FSGS

ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin II receptor blocker; CKD = chronic kidney disease; KDIGO = Kidney Disease Improving Global Outcomes.

1. KDIGO Clinical Practice Guidelines for Glomerulonephritis. *Kidney Int Suppl.* 2012;2:135.

New Therapeutic Strategy: Endothelin (ET-1) Blockade

Preclinical studies

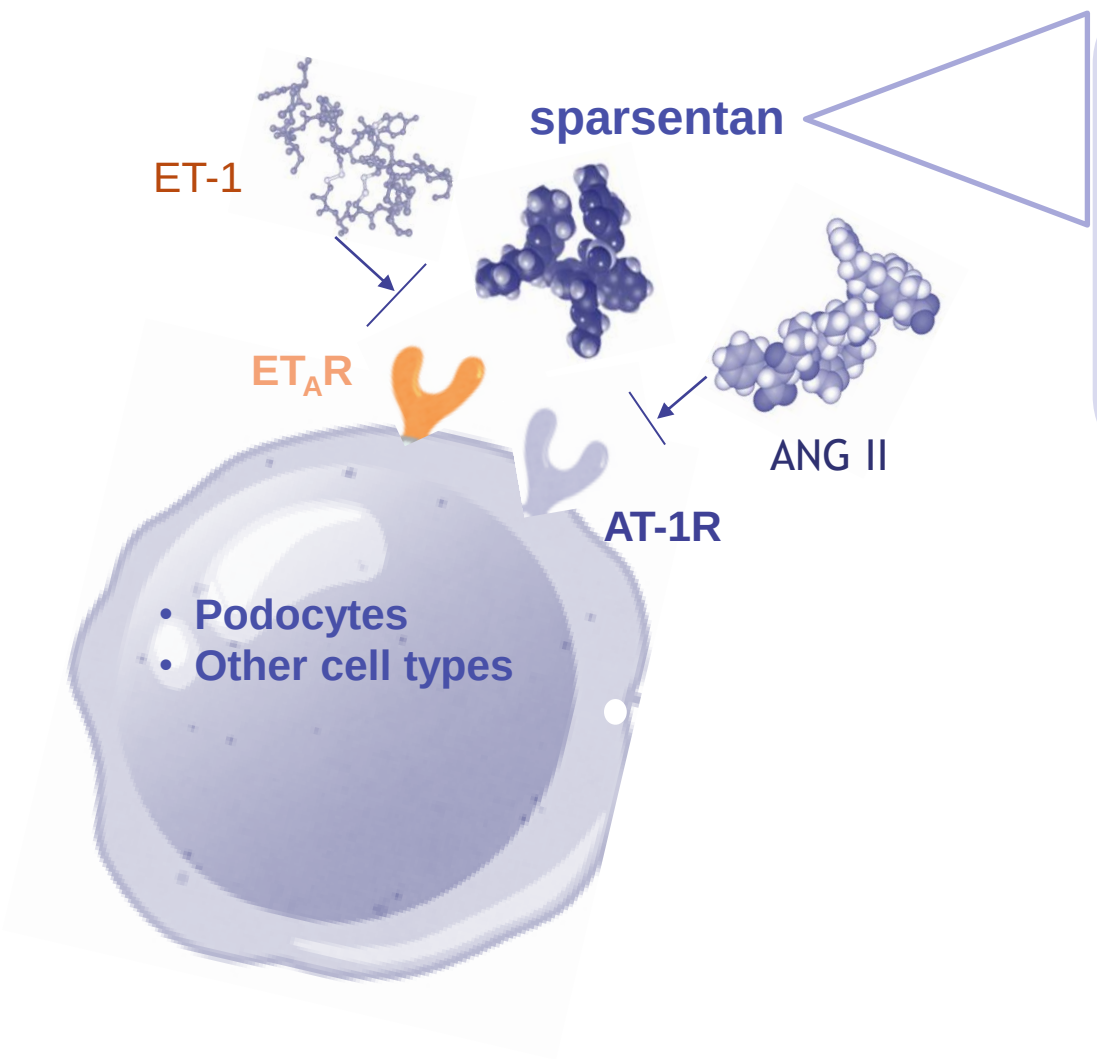


Clinical studies

- Endothelin antagonists showed anti-proteinuric effect
  - Short-term studies in diabetic nephropathy and other proteinuric CKD
- No large-scale studies focused on primary FSGS

CKD = chronic kidney disease; ET-1 = endothelin 1

Sparsentan: Dual Mechanism of Action



- Small-molecule drug
- First-in-class therapy
- Target specificity: highly selective antagonist of angiotensin type 1 (AT-1) and endothelin type A (ET_A) receptors

ANG II = angiotensin II; AT-1R = angiotensin II type 1 receptor; ET-1 = endothelin 1; ET_AR = endothelin type A receptor.

Kowala MC, et al. *J Pharmacol Exp Ther.* 2004;309:275–284.

Hypothesis and Objective: DUET Trial

Hypothesis

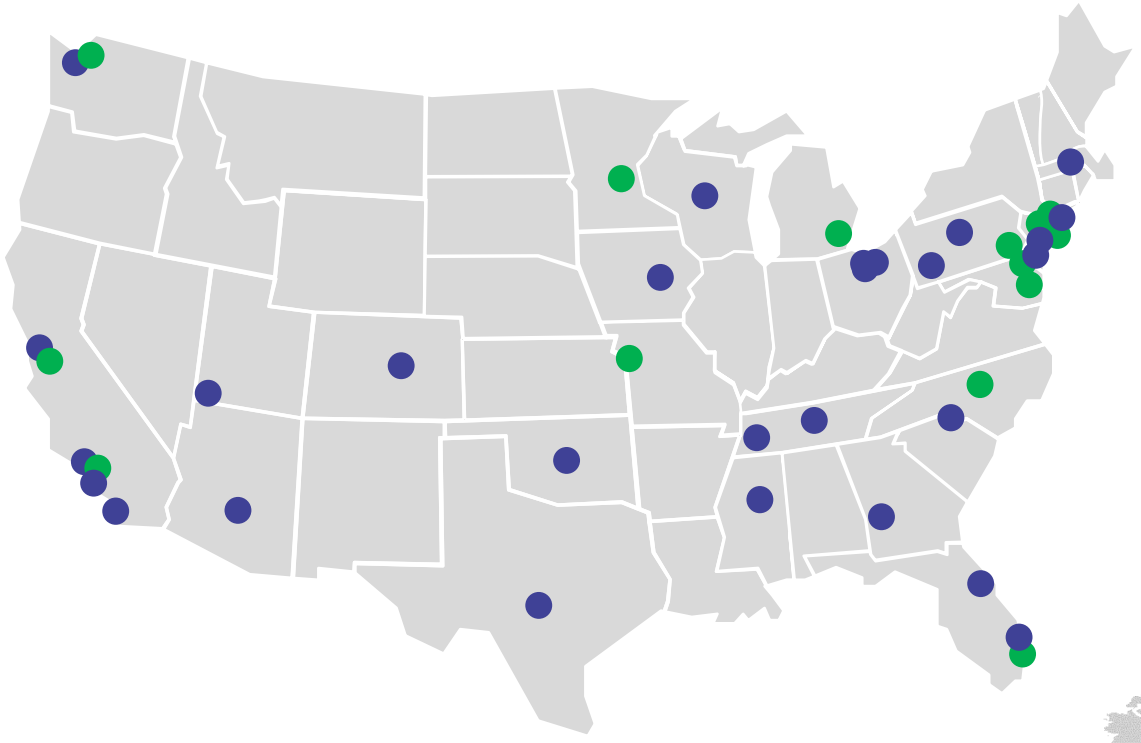
Dual blockade of AT-1 and ET_A receptors in patients with primary FSGS reduces proteinuria greater than blockade of AT-1 receptor alone

Objective

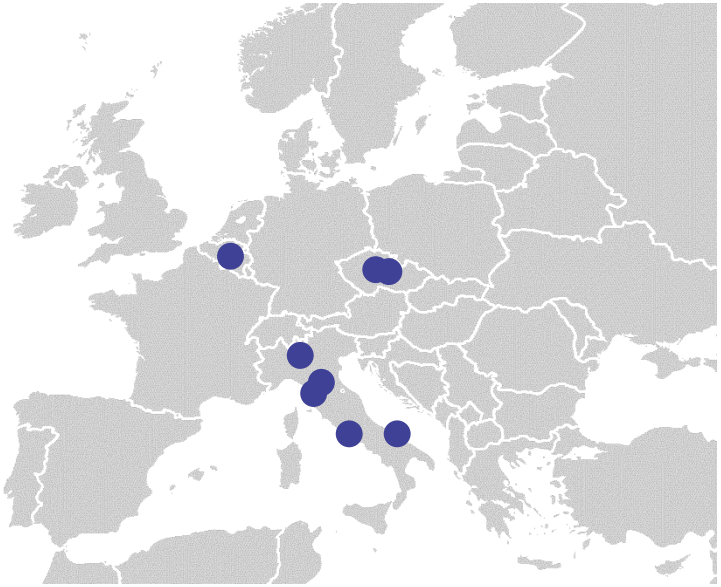
To evaluate the efficacy and safety of sparsentan, as compared with irbesartan, to reduce proteinuria in patients with primary FSGS during an 8-week, double-blind study period and an open-label extension

DUET Trial Design

DUET Clinical Sites



DUET site
DUET + NEPTUNE site*



- One of the largest FSGS studies completed
  - 48 sites in 4 countries consented and/or enrolled patients
- Approved ancillary study of NEPTUNE

*NEPTUNE sites shown are only those who were also DUET sites.
DUET study sites: https://clinicaltrials.gov/ct2/show/study/NCT01613118?term=duet+study&rank=4&show_locs=Y#locn
NEPTUNE study sites: http://www.neptune-study.org/

Patient Selection

Inclusion criteria

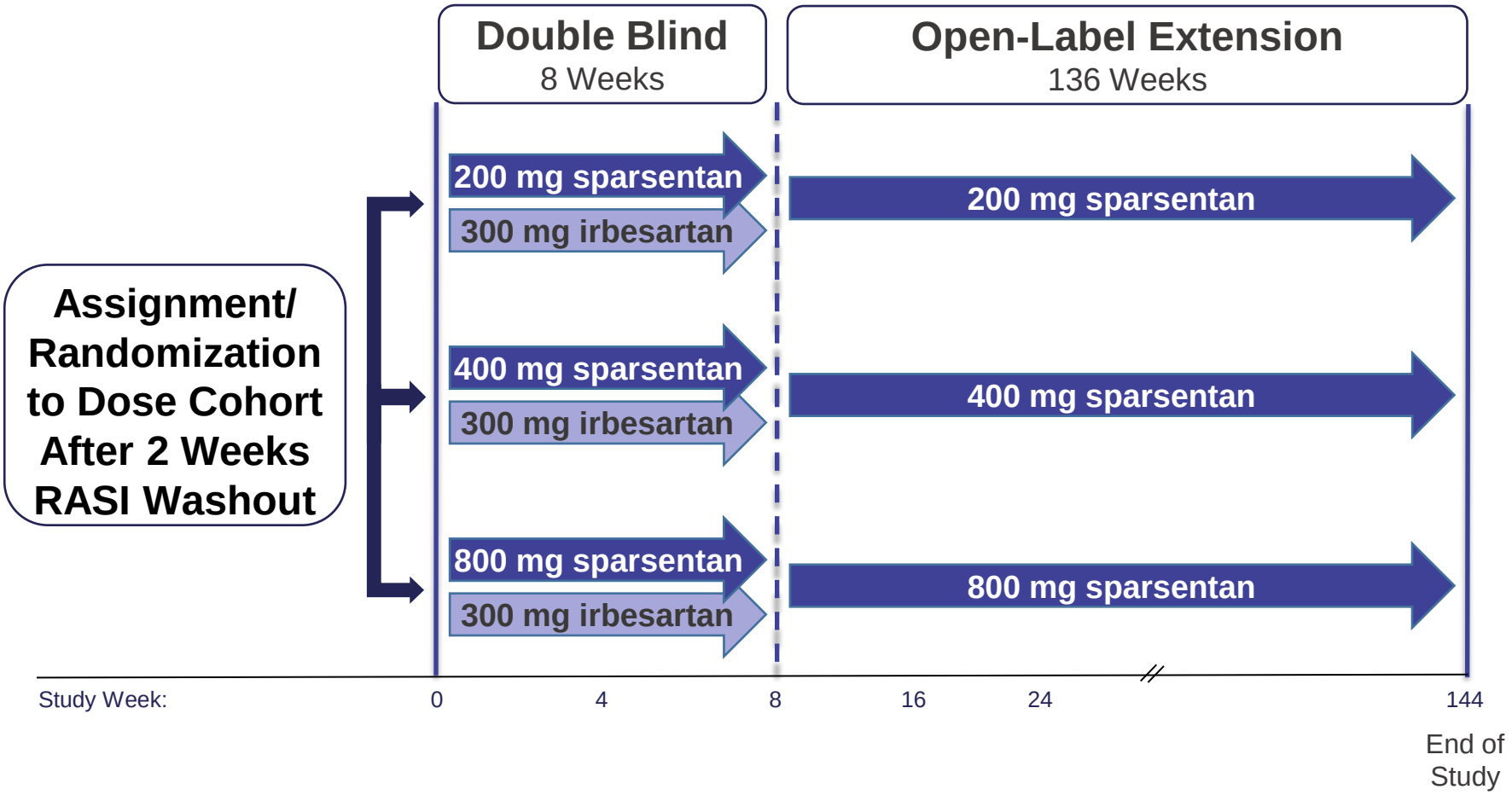
- US sites: patients aged 8–75 years
- EU sites: patients aged 18–75 years
- Biopsy-proven primary FSGS or documented genetic mutation
- Urinary protein-to-creatinine ratio (UPC) ≥ 1.0 g/g
- eGFR > 30 mL/min/1.74 m^2
- Mean seated BP > 100/10 mmHg and < 145/96 mmHg for patients aged 18 years or older
- For patients aged < 18 years of age, mean seated BP > 90/60 mmHg and < 95th percentile for age, gender, and height
- Stable dose of immunosuppressive medication for ≥ 1 month

Exclusion criteria

- Secondary FSGS
- Significant medical conditions related to cardiac, hepatic, or immune function
- Body mass index > 40 mg/m^2 for adults or in the 99th percentile plus 5 for pediatric patients
- Hematocrit < 27% or hemoglobin < 9 m/dL
- Serum potassium > 5.5 mEq/L
- Women who were pregnant, breastfeeding, or of child-bearing potential who were unwilling to use 2 methods of contraception

BP = blood pressure; eGFR = estimated glomerular filtration rate; EU = European Union; US = United States.

DUET Dose Cohorts



Patients were assigned to dose cohort, then randomized to sparsentan or irbesartan within the dose cohort
Study drug administered orally, once daily. Patients who weighed < 50 kg received half of the daily dose of sparsentan or irbesartan according to the assigned dose cohort.
RASI = renin-angiotensin system inhibitor.

Endpoints and Statistical Analysis

Endpoints

- **Primary**
  - Percent change in UPC from baseline to week 8
- **Key secondary**
  - Modified partial remission
    - Proportion of patients who achieved UPC ≤ 1.5 g/g and a > 40% reduction in UPC from baseline to week 8
- **Key tertiary**
  - Blood pressure
  - eGFR
  - Laboratory results
- **Safety**
  - Incidence of adverse events

Statistical Analysis

- **Efficacy analyses performed on the efficacy evaluable set (EES)**
  - Patients who received at least 1 dose of study drug and had both baseline and week 8 UPC values
  - Prespecified analysis order:
    - All sparsentan doses vs irbesartan
    - Sparsentan 800- and 400-mg doses vs irbesartan
    - Sparsentan 400-mg dose vs irbesartan
    - Sparsentan 800-mg dose vs irbesartan

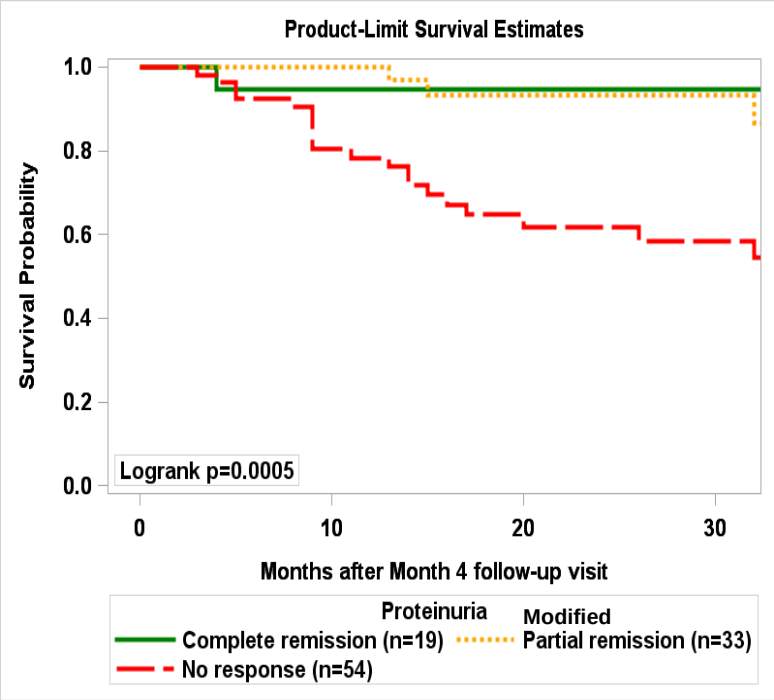
eGFR = estimated glomerular filtration rate; UPC = urinary protein-to-creatinine ratio.

Secondary Endpoint: Modified Partial Remission

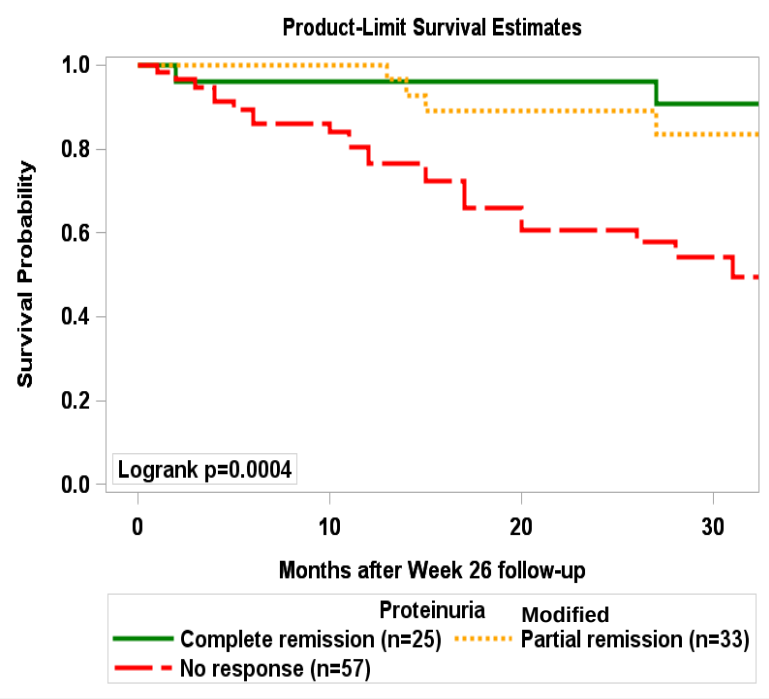
- Endpoint based on data from the Nephrotic Syndrome Study Network (NEPTUNE) and FSGS Clinical Trial (FSGS-CT)[1]
  - Complete remission: UPC < 0.3 g/g
  - Modified partial remission: UPC < 1.5 g/g and 40% reduction in UPC

Proteinuria and Progression to Kidney Failure

NEPTUNE



FSGS-CT



1. Troost JP, et al. A Clinical Outcome Assessment of Proteinuria in Patients with Focal Segmental Glomerulosclerosis. American Society of Nephrology Kidney Week; 2016. Abstract #FR-OR117.

Results

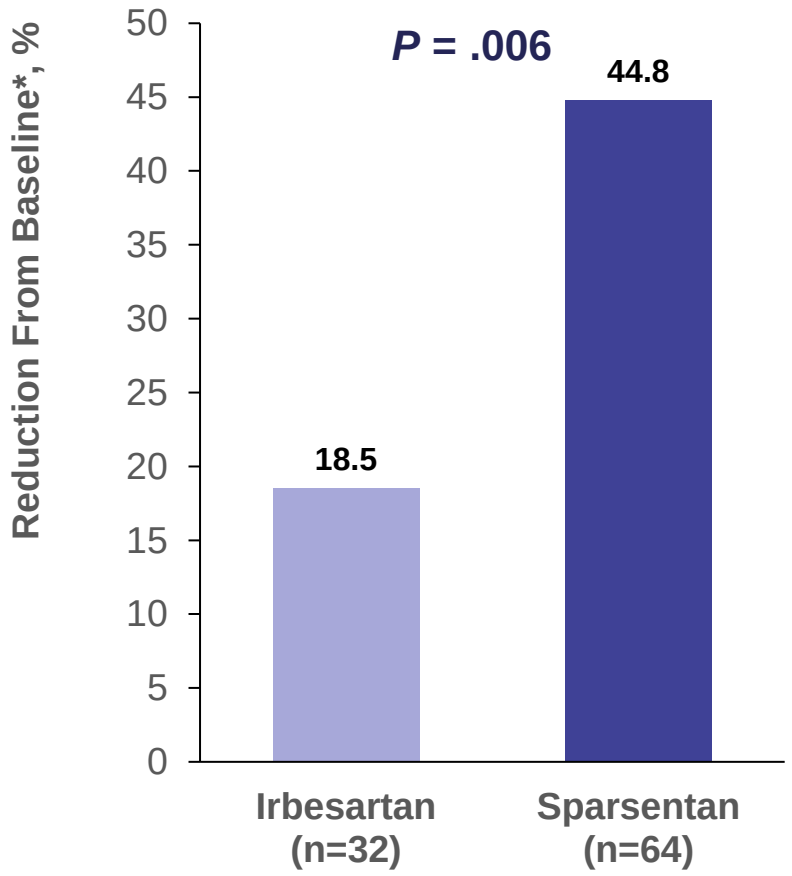
Baseline Characteristics

	Irbesartan (n=32)	Sparsentan, all doses (n=64)
Age, n (%)		
Pediatric (aged 8-18)	8 (25)	12 (19)
Adult (aged 19-75)	24 (75)	52 (81)
Sex, n (%)		
Female	14 (44)	27 (42)
Male	18 (56)	37 (58)
Race, n (%)		
Asian	1 (3)	4 (6)
Black	6 (19)	6 (9)
White	23 (72)	51 (80)
Other	2 (6)	3 (5)
Ethnicity, n (%)		
Hispanic/Latino	5 (16)	13 (20)
Non-Hispanic/Non-Latino	27 (84)	51 (80)
BMI kg/m^2, mean (SD)	28.1 (6.2)	28.4 (6.0)
ACEI or ARB use before washout, n (%)	25 (78)	52 (81)
Immunosuppressant use, n (%)	13 (36)	21 (29)
Corticosteroids	4 (11)	14 (19)
Calcineurin inhibitors	5 (14)	9 (12)
Mycophenolate mofetil	7 (19)	6 (8)
Other	0	1 (1)
eGFR, mL/min/1.73m^2, mean (SD)	73.1 (43.1)	72.8 (36.5)
UPC, g/g, median (SD)	3.27 (2.67)	3.62 (3.78)
Nephrotic-range/proteinuria (at Visit 3; UPC > 3.5 g/g), n (%)	14 (44)	33 (52)

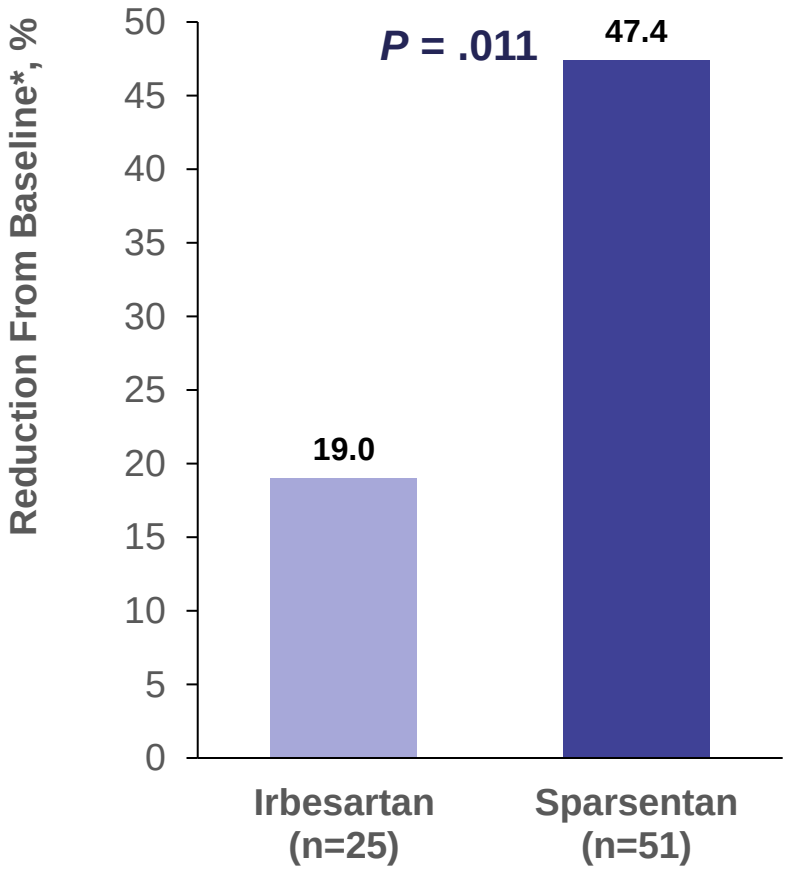
ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; SD = standard deviation.

Reduction in UPC from Baseline to Week 8

All Sparsentan Doses (200 mg, 400 mg, 800 mg)



400-mg and 800-mg Sparsentan Doses



*Geometric least squares mean reduction.
P values from analysis of covariance. Analyses based on the EES.

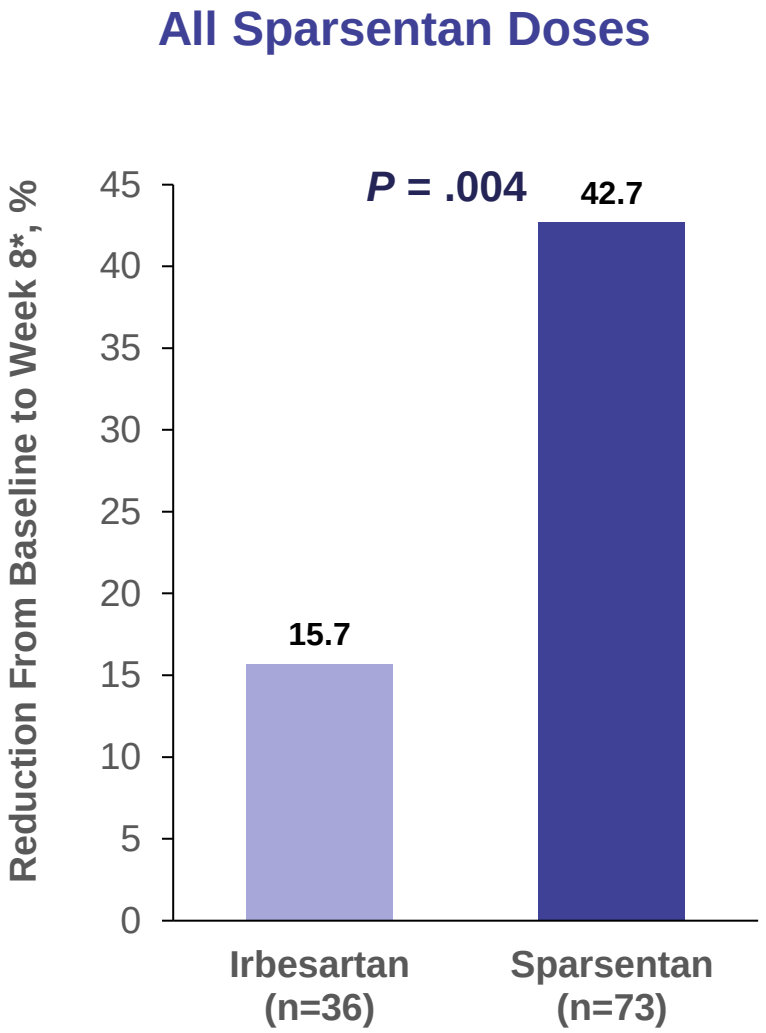
Reduction in UPC from Baseline to Week 8 (cont'd)

Sparsentan Dose Cohort	Reduction from Baseline*, %		
	Irbesartan (n=32)	Sparsentan (n=64)	*P* value
All doses	**18.5** (n=32)	**44.8** (n=64)	.006
400 mg and 800 mg	**19.0** (n=25)	**47.4** (n=51)	.011
200 mg	**15.0** (n=7)	**33.1** (n=13)	.298
400 mg	**28.1** (n=17)	**52.7** (n=21)	.056
800 mg	**9.3** (n=8)	**41.3** (n=30)	.127

*Geometric least squares mean reduction.
P values from analysis of covariance. Analyses based on the EES.

Intent-to-Treat Analysis of UPC

- Baseline or week 8 UPC data were missing for 9 sparsentan-treated patients and 4 irbesartan-treated patients
- Missing data imputed as zero change



*Geometric least squares mean reduction.
P value from analysis of covariance. Analyses based on the full analysis set.

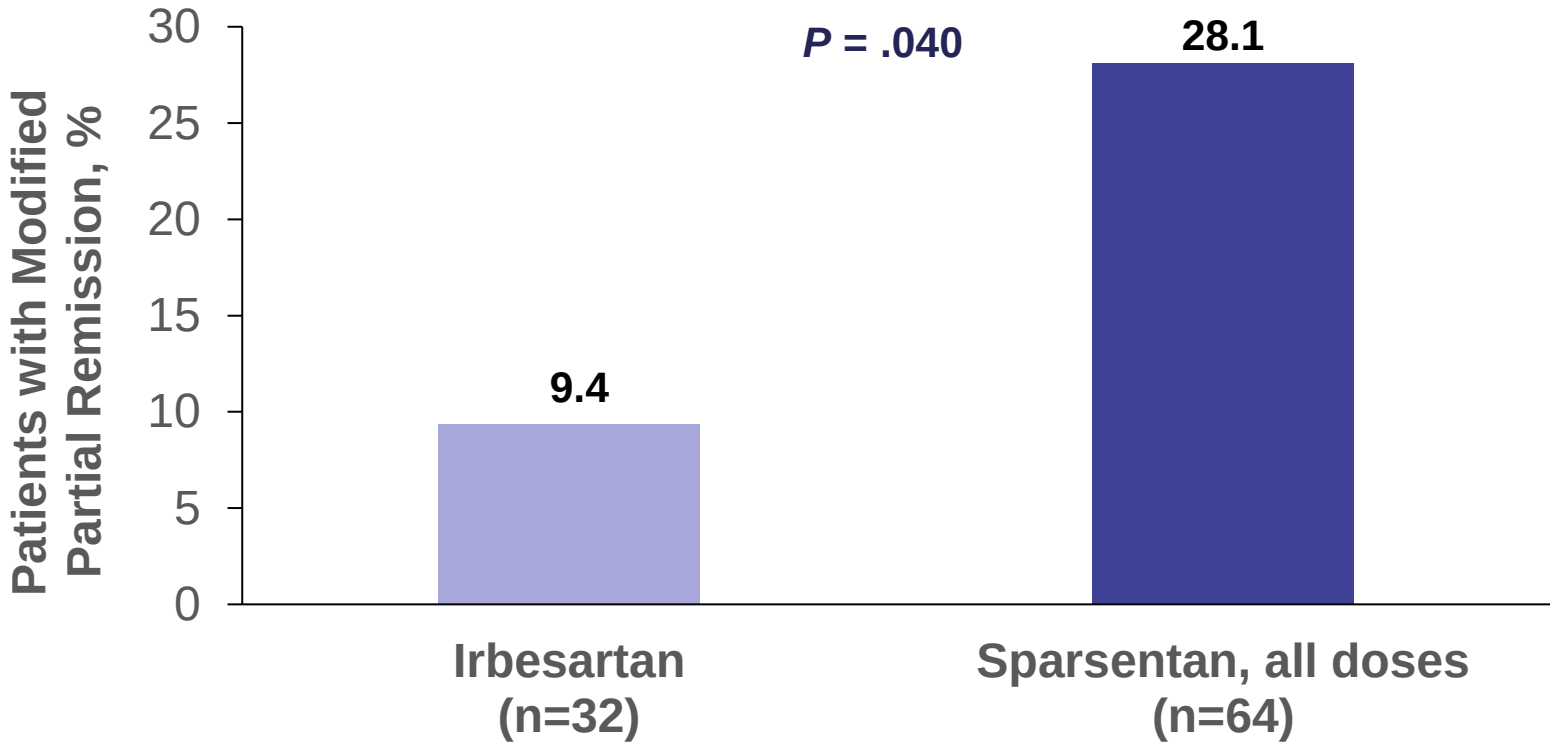
Intent-to-Treat Analysis of UPC (cont'd)

Sparsentan Dose Cohort	Reduction from Baseline*, %		
	Irbesartan (n=36)	Sparsentan (n=73)	*P* value
All doses	**15.7** (n=36)	**42.7** (n=73)	.004
400 mg and 800 mg	**15.9** (n=28)	**44.8** (n=60)	.008
200 mg	**13.2** (n=8)	**33.1** (n=13)	.227
400 mg	**23.6** (n=20)	**50.5** (n=26)	.033
800 mg	**9.7** (n=8)	**38.4** (n=34)	.161

*Geometric least squares mean reduction.
P values from analysis of covariance. Analyses based on the full analysis set.

Modified Partial Remission At 8 Weeks

- Modified partial remission defined as UPC ≤ 1.5 g/g and > 40% reduction in UPC

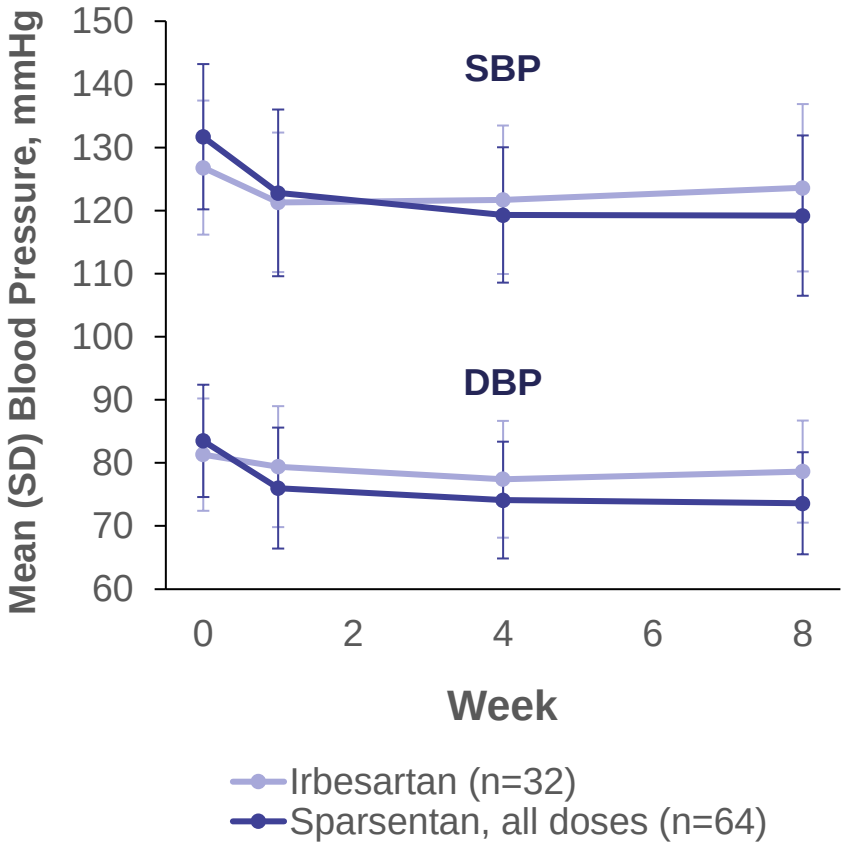


Complete remission (UPC < 0.3 g/g) was achieved by 4 sparsentan-treated patients vs 0 irbesartan-treated patients

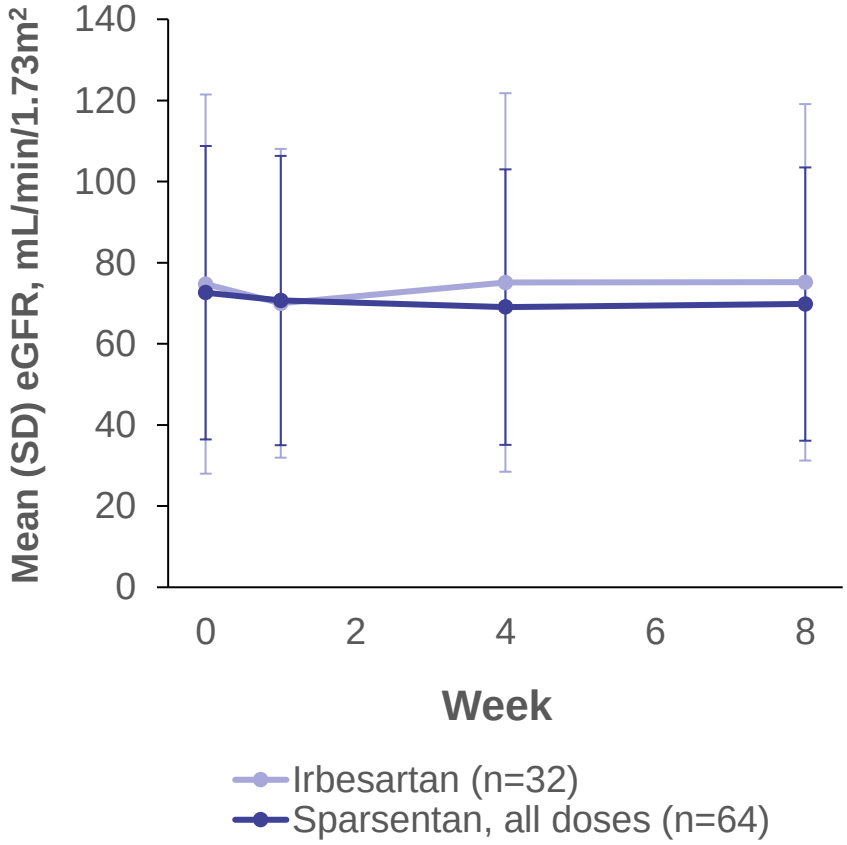
P value from Fisher's exact tests. Analyses based on the EES.

Blood Pressure and eGFR

Blood Pressures at Each Visit



eGFR at Each Visit



There were also no statistically significant changes in serum potassium, N-terminal pro-B-type natriuretic peptide, or albumin

DBP = diastolic blood pressure; SBP = systolic blood pressure; SD = standard deviation.
Analyses based on the EES.

Safety

Treatment-Emergent Adverse Events (TEAEs)

TEAE	Patients with TEAEs During the Double-Blind Period, %	
	Irbesartan (n=36)	Sparsentan, All Doses (n=73)
Any	72.2	76.7
Drug-related	36.1	43.8
Serious	2.8	2.7
Leading to dose change or interruption	8.3	23.3
Leading to drug discontinuation	2.8	4.1
Leading to study withdrawal	2.8	2.7
Death	0	0

TEAEs With Incidence > 5%

	Patients with TEAEs with Incidence > 5% During the Double-Blind Period, %	
Preferred Term	**Irbesartan (n=36)**	**Sparsentan, All Doses (n=73)**
Headache	19.4	19.2
Hypotension/orthostatic hypotension	8.3	16.4
Dizziness	11.1	13.7
Edema/edema peripheral	2.8	12.3
Nausea	8.3	12.3
Diarrhea	2.8	8.2
Vomiting	2.8	8.2
Upper abdominal pain	5.6	5.5
Cough	5.6	4.1
Fatigue	11.1	4.1
Nasal congestion	11.1	2.7
Upper respiratory tract infection	5.6	2.7
Muscle spasms	5.6	0

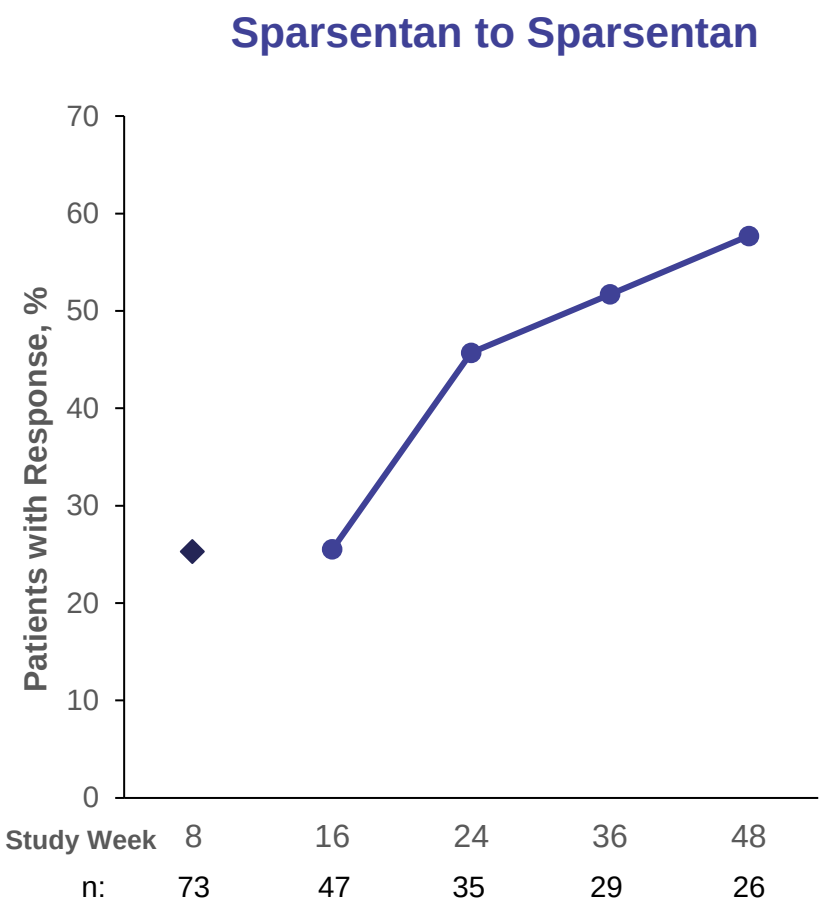
Edema Incidence and Severity

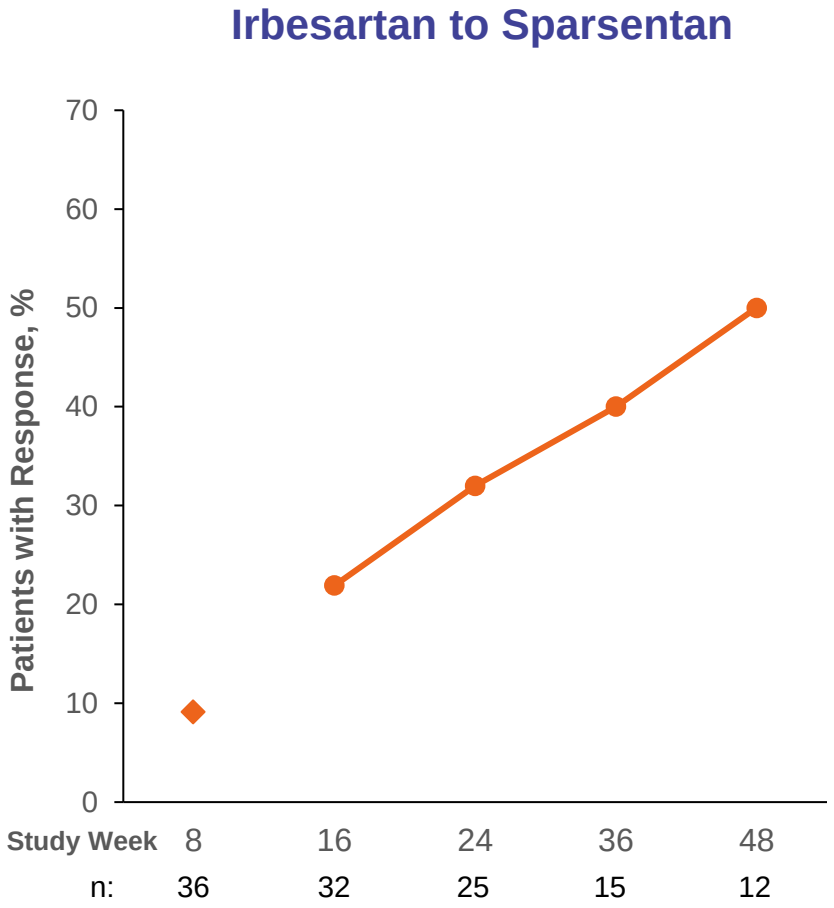
Edema Severity Grade	Patients with Edema During the Double-Blind Period, %			
	Irbesartan		Sparsentan, All Doses	
	Baseline (n=29)	Week 8 (n=28)	Baseline (n=53)	Week 8 (n=60)
0	76	86	66	65
1+ to 2+	21	14	32	30
3+ to 4+	3	0	2	5

P value = NS

Open-Label Period

Modified Partial Remission During the Open-Label Period





◆ ◆ 24-hour UPC measurements at week 8

● ● First morning void (spot measure) UPC on weeks 16 to 48

Response defined as UPC ≤ 1.5 g/g and > 40% reduction in UPC (first morning void) from baseline. Baseline in the double-blind period defined as week 0; baseline for the open-label period defined as last observation before start of open-label sparsentan treatment (ie, week 8). 46% of sparsentan-treated patients provided spot measure (first morning void) at week 8. Percent of patients that provided spot measure (first morning void) at week 8 is not available for irbersartan-treated patients. Based on the full analysis set.

Strengths and Limitations

- Strengths
  - One of the largest studies in FSGS
  - Geographically broad and clinically diverse FSGS population studied
  - Consistent with current treatment recommendations
- Limitations
  - Relative scarcity of available patients in rare disease trials
  - Short duration of double-blind treatment period
  - Research focusing on understanding of proteinuria as a surrogate endpoint is ongoing

Conclusions

- Sparsentan achieved a significant reduction in proteinuria compared with irbesartan in patients with FSGS, as measured by the change from baseline to 8 weeks post-randomization
- The proportion of patients who achieved a modified partial response (UPC ≤ 1.5 g/g and > 40% reduction in UPC) was significantly greater in the sparsentan-treated group and increased throughout the open-label period
- Sparsentan was generally safe and well-tolerated
  - 84% of patients who completed the 8-week double-blind period remain on sparsentan in the open-label extension

Thank You to the DUET Physicians, Coordinators, and Patients

PI Name	Location	PI Name	Location	PI Name	Location	PI Name	Location
Adler, Sharon	Torrance, CA	Elliott, Matthew	Charlotte, NC	Kusnir, Jorge	Winter Park, FL	Radhakrishna, Jai	New York, NY
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Ali, Nausheen	La Palma, CA	Feig, Daniel	Birmingham, AL	Lieberman, Kenneth	Hackensack, NJ	Raina, Rupesh	Akron, OH
Baranski, Joel	San Diego, CA	Fornoni, Alessia	Miami, FL	Marder, Brad	Denver, CO	Rheault, Michelle	Minneapolis, MN
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Egidi, Maria	Pisa, Italy	Hogan, Jonathan	Philadelphia, PA	Paredes, Ana	Miami, FL	Woroniecki, Robert	Head of the Harbor, NY
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