Antiproteinuric Effect of Sparsentan, A Dual Angiotensin II and Endothelin Type A Receptor Antagonist, in Patients With Primary Focal Segmental Glomerulosclerosis (FSGS): A Subgroup Analysis of the DUET Trial

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Disclosures

Loreto Gesualdo, MD, FERA	• Study investigator for Retrophin, Inc
Kenneth Lieberman, MD	• Received honoraria for speaking for Alexion and Mallinckrodt • Study investigator for Retrophin, Inc
Vladimir Tesar, MD, PhD, PhD, FERA, FASN	• Study investigator for Retrophin, Inc
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Radko Komers, MD	• Employee of Retrophin, Inc. Owns stock/stock options

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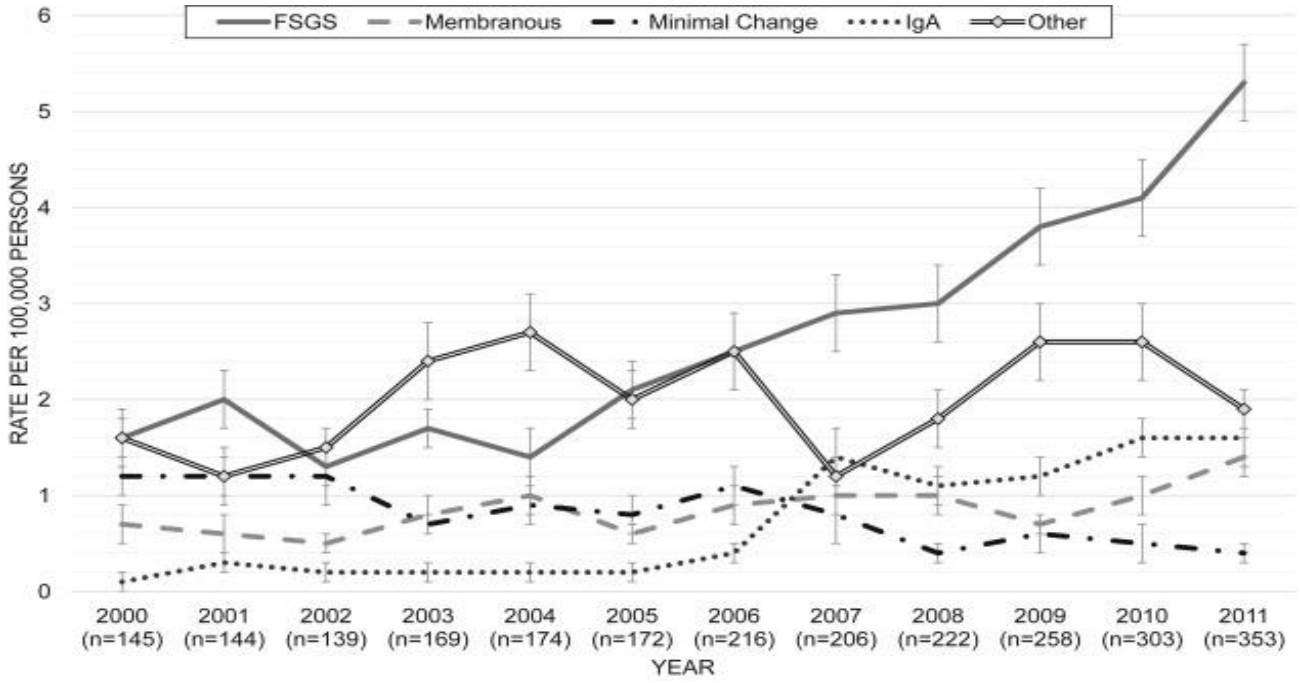
Background

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]

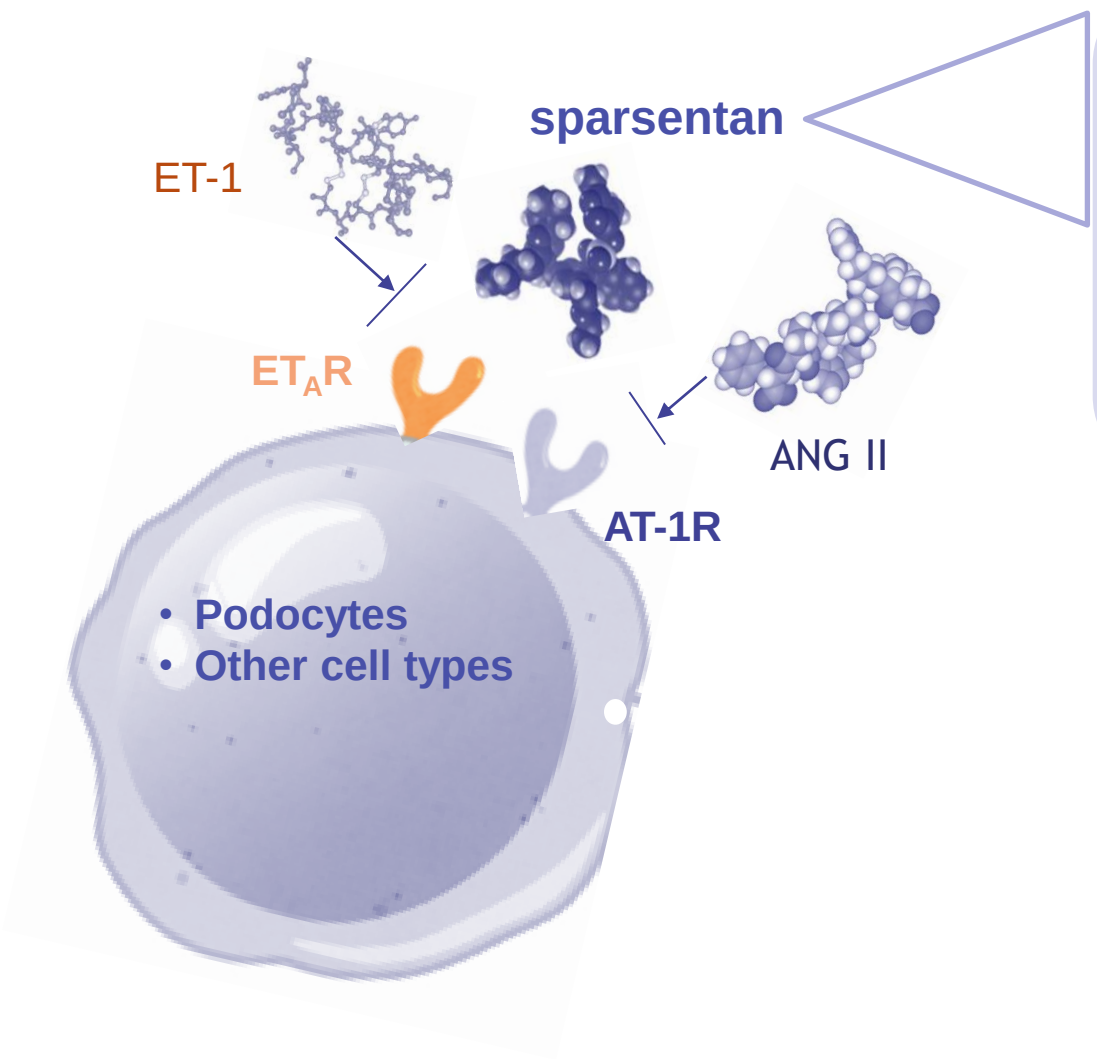


  - Approximately half of patients with nephrotic-range proteinuria will require renal replacement therapy within 5–10 years of diagnosis[3]
  - Significant unmet need for therapy

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.

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.

DUET STUDY

Study 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

Patient Selection

Inclusion criteria

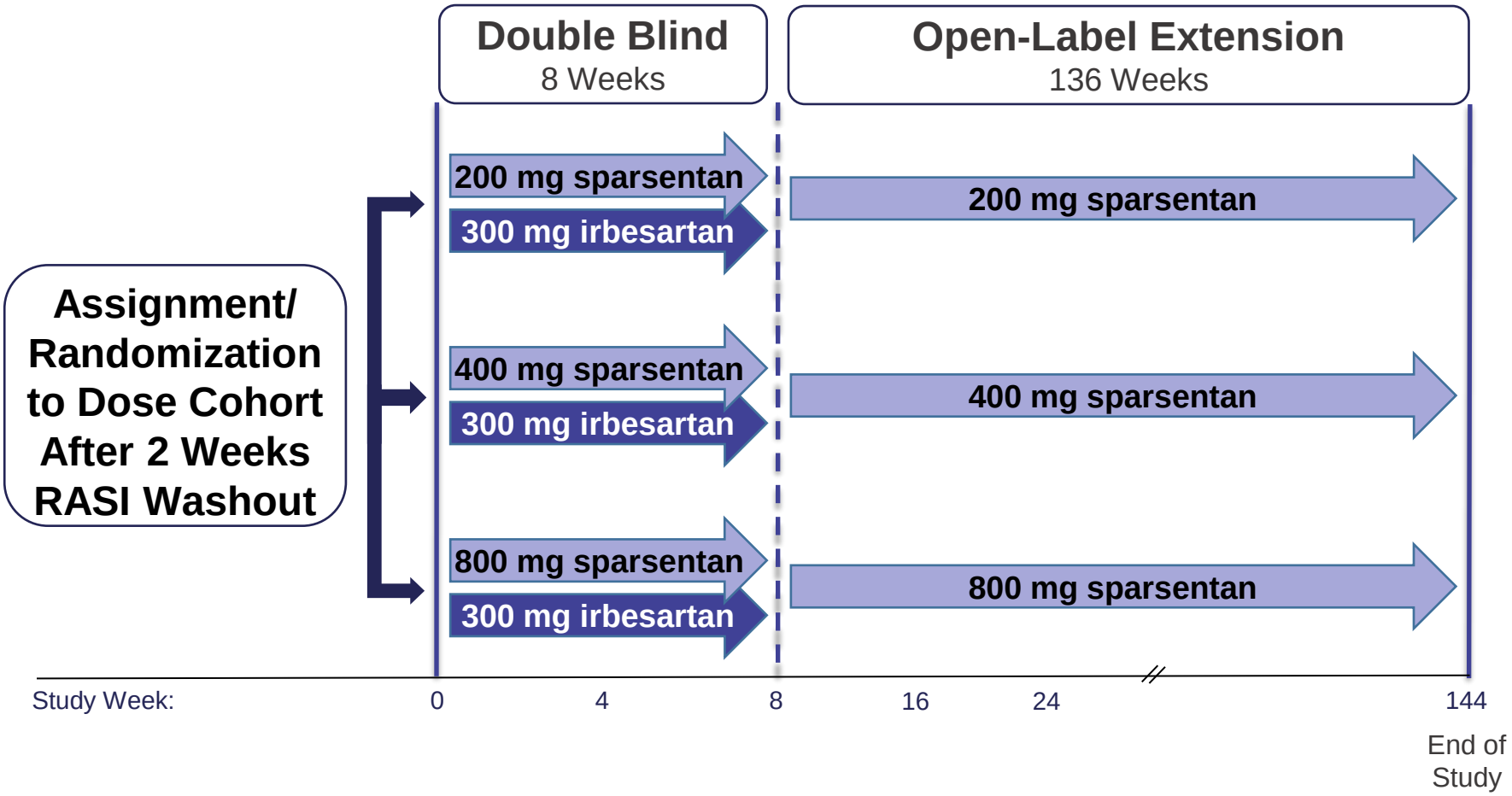
- US sites: patients aged 8–75 years
- EU sites: patients aged 18–75 years
- Biopsy-proven primary FSGS or documented genetic mutation
- Urinary protein-to-creatinine ratio (UPC) ≥1.0 g/g
- eGFR >30 mL/min/1.73 m^2
- Mean seated BP >100/60 mmHg and <145/95 mmHg for patients aged 18 years or older
- For 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.

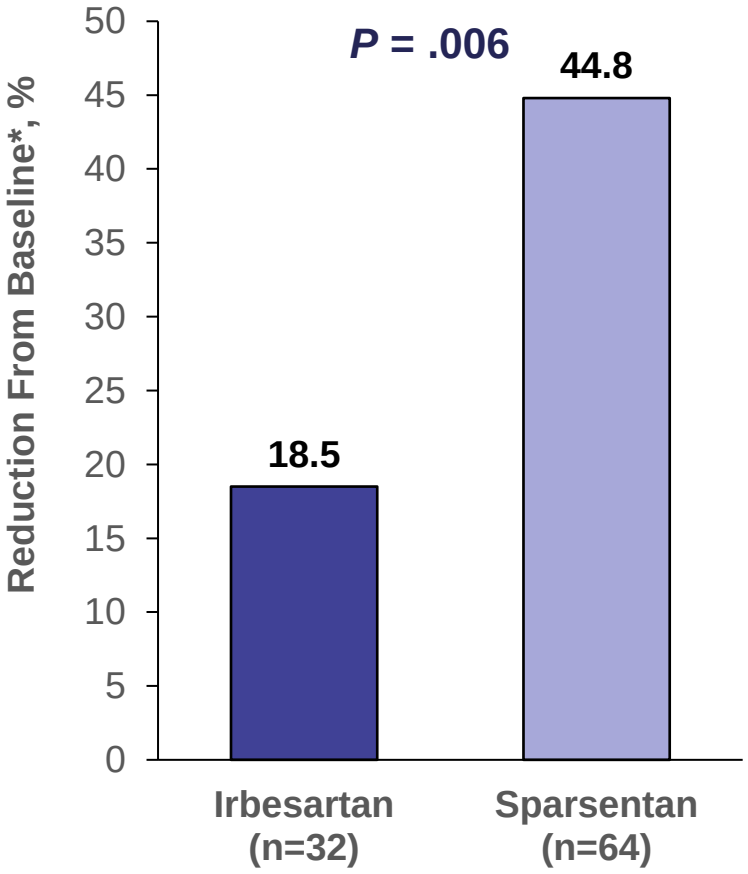
Baseline Characteristics

	Irbesartan (n=32)	Sparsentan, all doses (n=64)
Age, n (%)		
Pediatric (aged 8-18 years)	8 (25)	12 (19)
Adult (aged 19-75 years)	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/1.73 m^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)

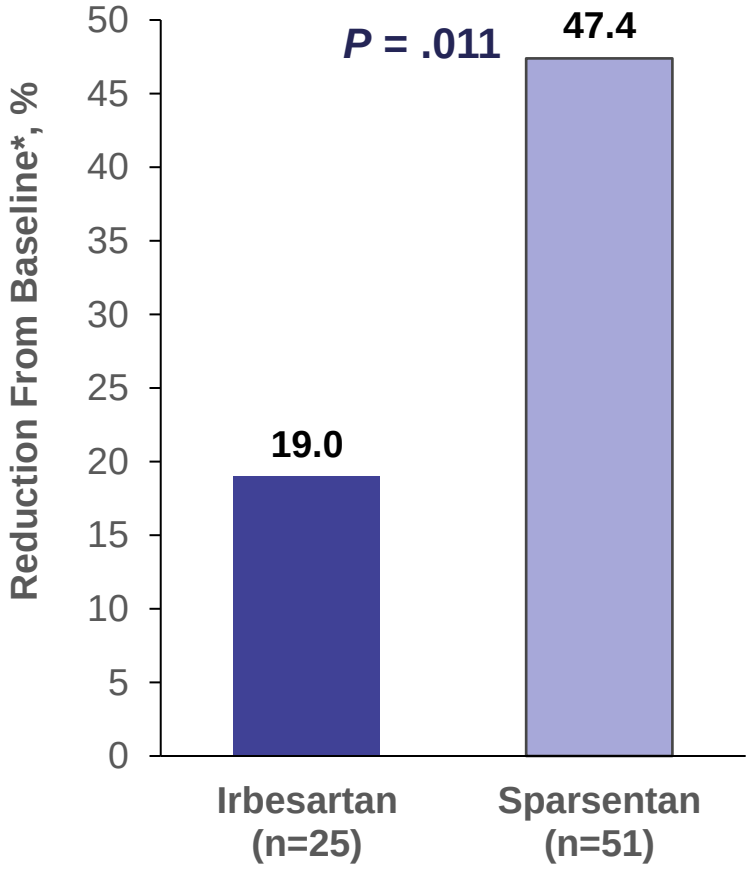
ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; SD = standard deviation.

DUET Study – Reduction in UPC from Baseline to Week 8

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



Pooled 400-mg and 800-mg Sparsentan Doses



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

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

DUET Subgroup Analysis: Methods

DUET Subgroup Analysis Objective

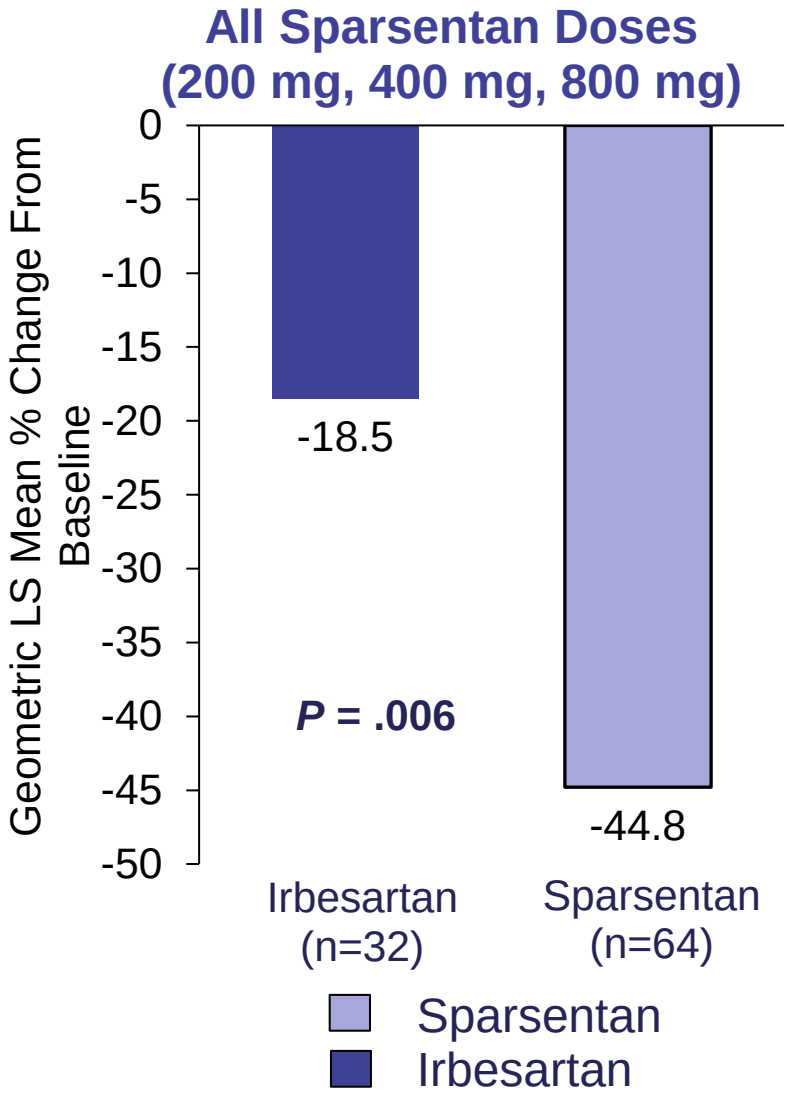
To evaluate the antiproteinuric effects of sparsentan and irbesartan in predefined subgroups of patients with FSGS based on prognostic factors

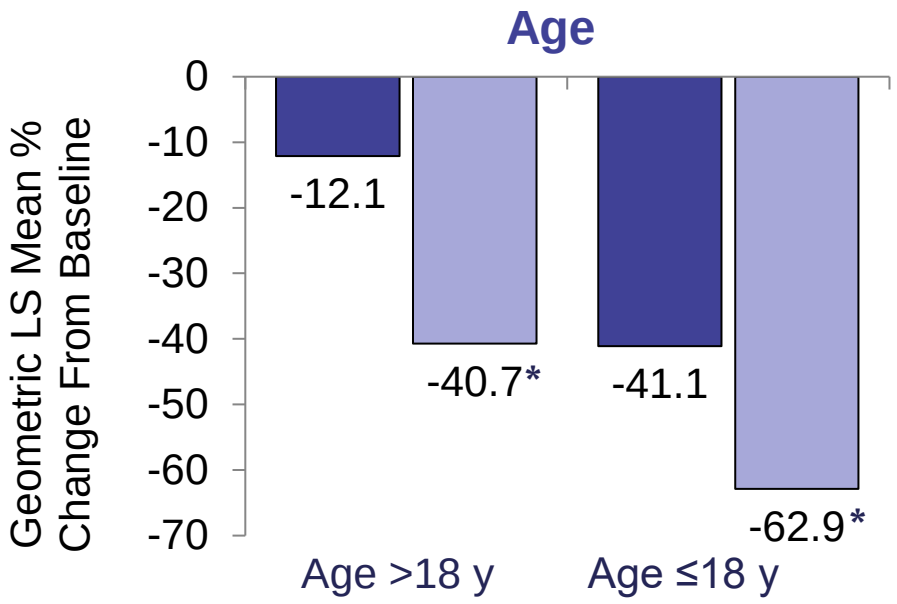
DUET Subgroup Analysis

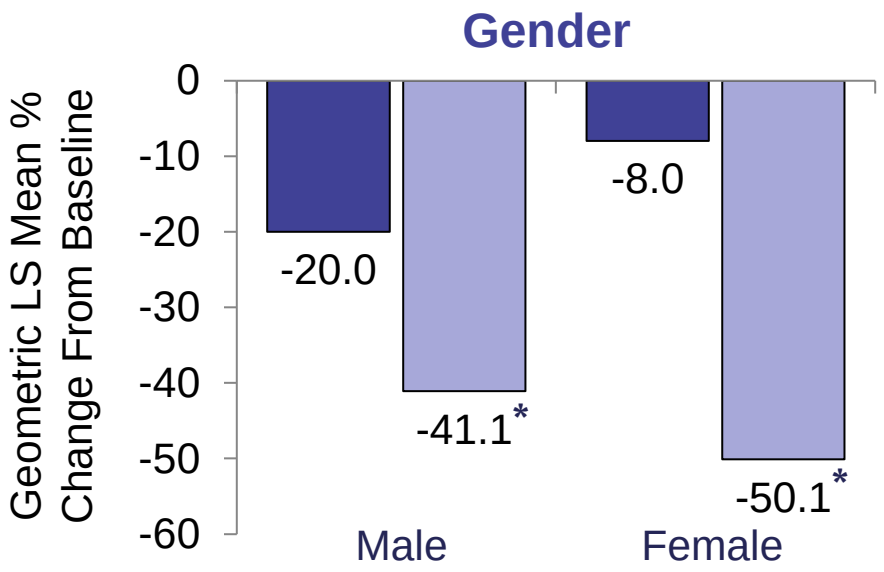
- Assessed changes from baseline to Week 8 in UPC for irbesartan- and sparsentan-treated patients stratified by prognostic factors:
  - Age
  - Gender
  - Race
  - Baseline proteinuria
  - Blood pressure
  - CKD stage
- Analyzed by Mixed-Effect Model Repeated Measures (MMRM) and within group analyses of changes from baseline
- No additional safety analyses were performed for the subgroups

Results

Percent Change in UPC (Non-nephrotic/Nephrotic) at Week 8 Adjusted for Prognostic Factors: Age and Gender

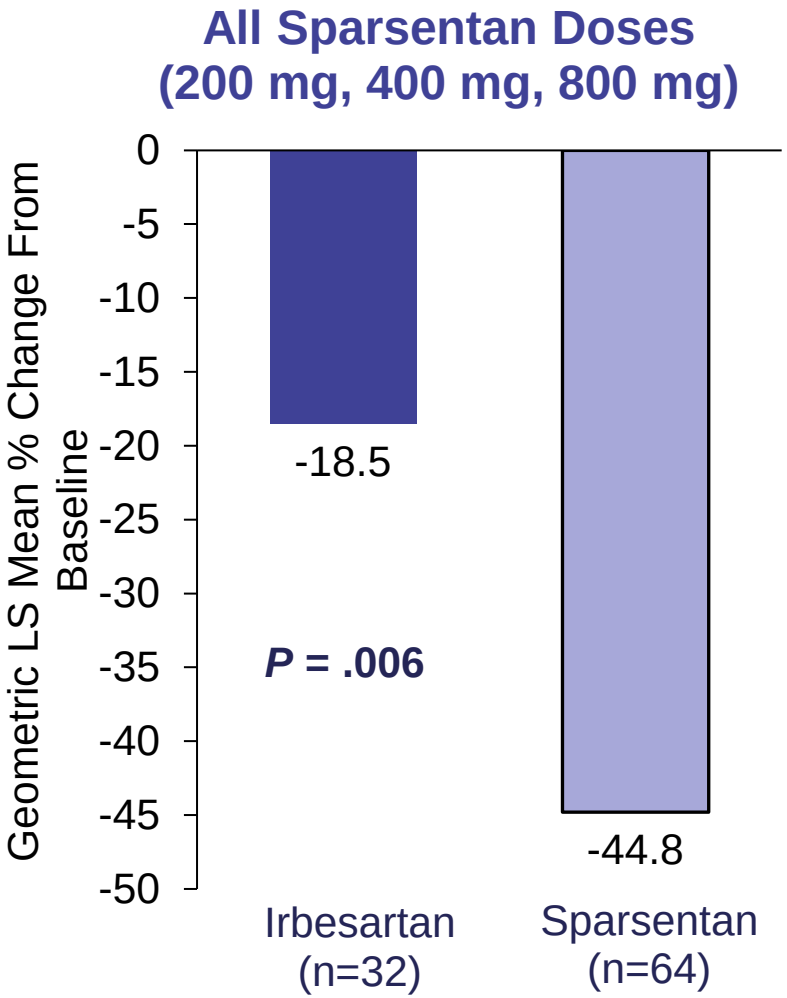


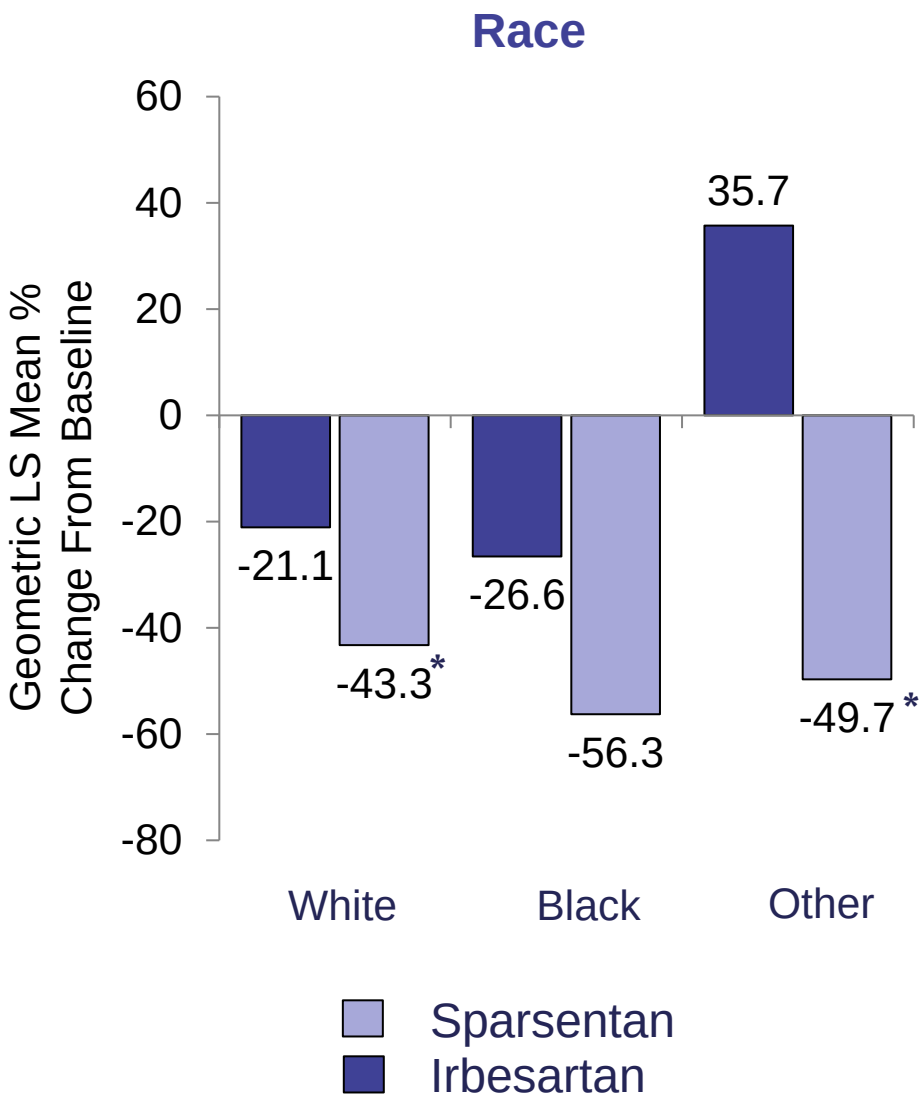




* *P*<.05 vs. baseline for all SPAR vs. IRB; MMRM p=NS

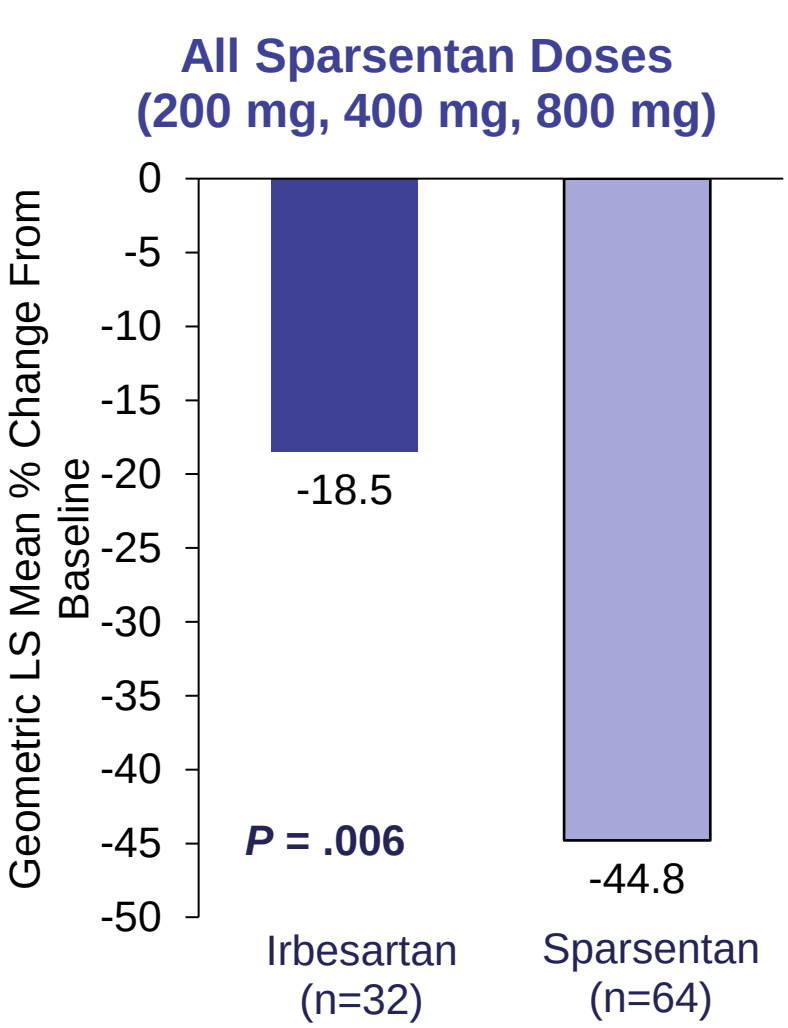
Percent Change in UPC (Non-nephrotic/Nephrotic) at Week 8 Adjusted for Prognostic Factors: Race

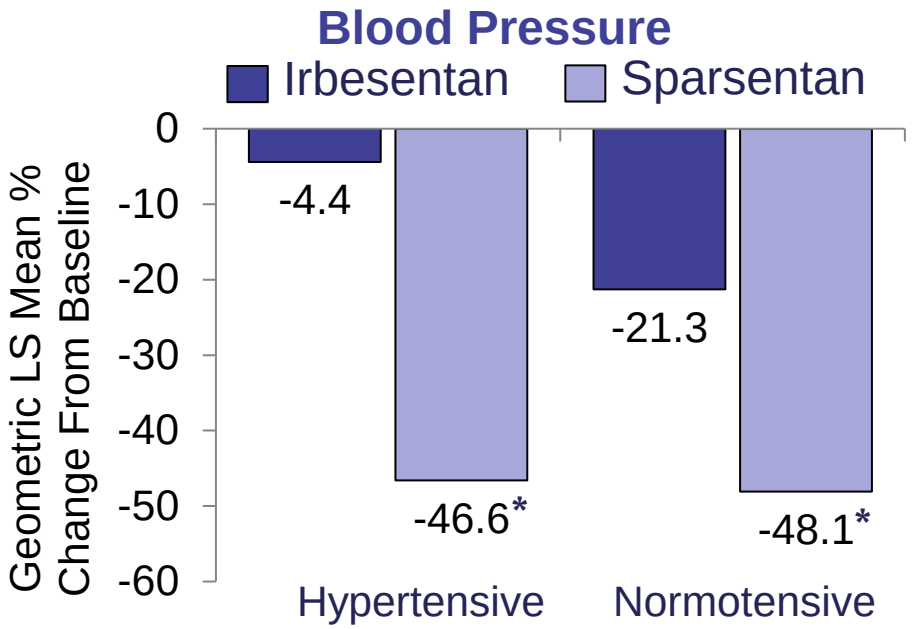


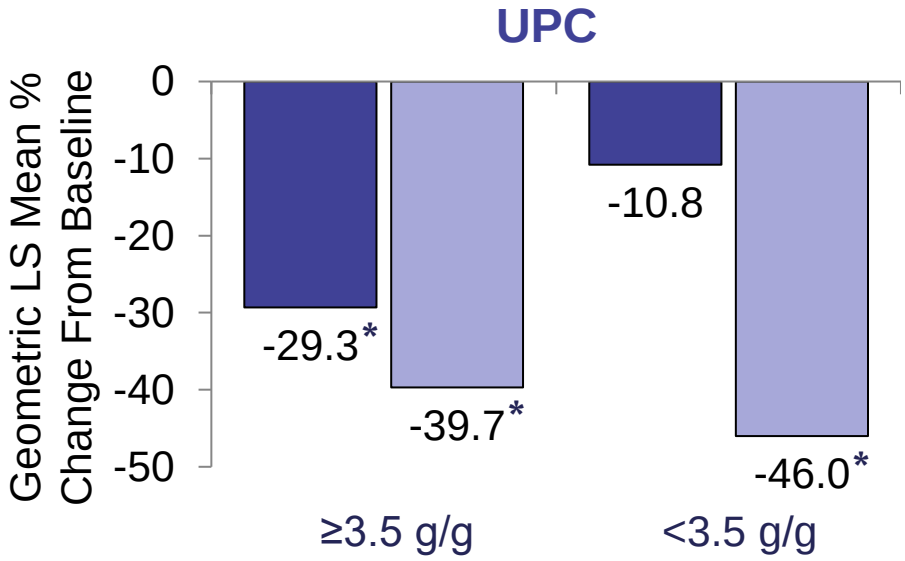


* *P*<.05 vs. baseline for all SPAR vs. IRB; MMRM p=NS

Percent Change in UPC (Non-nephrotic/Nephrotic) at Week 8 Adjusted for Prognostic Factors: Blood Pressure and UPC



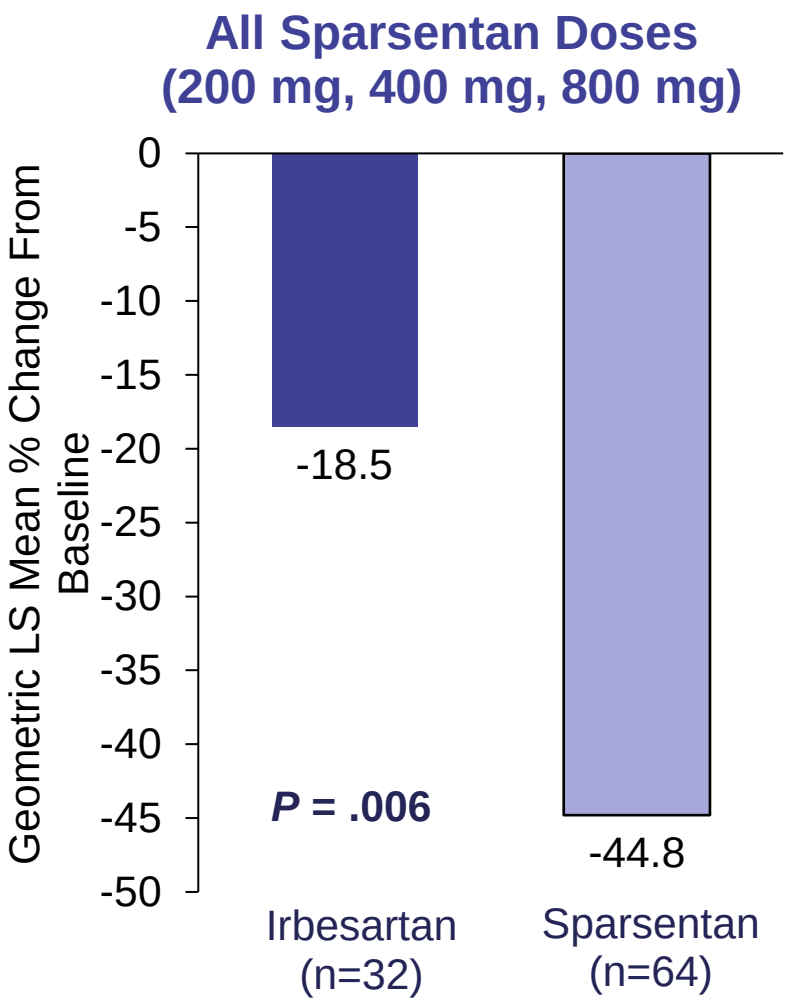


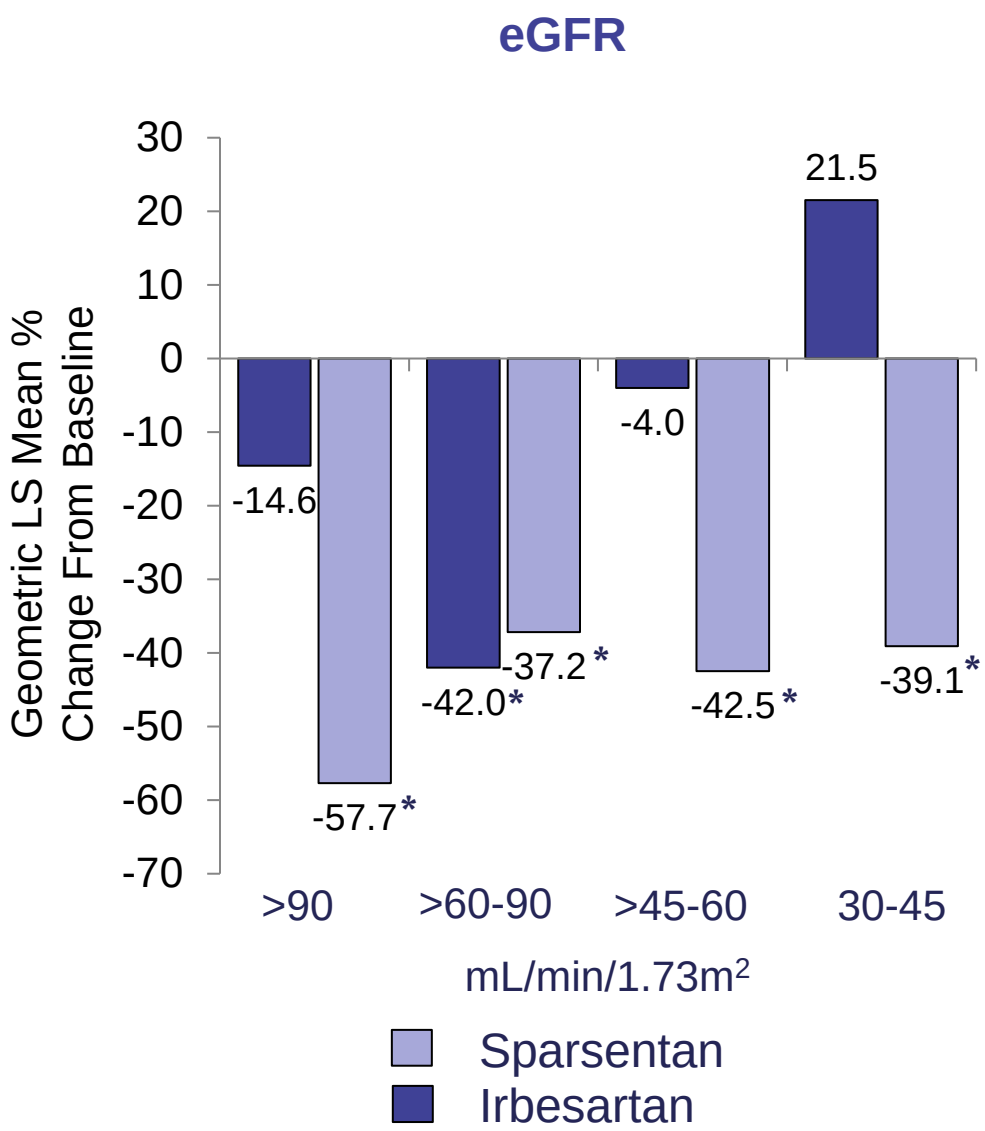


Hypertensive: SBP ≥140 mmHg or DBP ≥90 mmHg
Normotensive: SBP <140 mmHg and DBP <90 mmHg

* *P*<.05 vs. baseline for all SPAR vs. IRB; MMRM p=NS

Percent Change in UPC (Non-nephrotic/Nephrotic) at Week 8 Adjusted for Prognostic Factors: eGFR





* *P*<.05 vs. baseline for all SPAR vs. IRB; MMRM p=NS

Conclusions

- Compared to irbesartan, sparsentan-treated patients demonstrated significant decreases at Week 8 in UPC from baseline across almost all of the prespecified subgroups
- Although not powered for direct comparisons of antiproteinuric effects between sparsentan and irbesartan in subgroups, these observations suggest that sparsentan reduced UPC to a greater degree compared with irbesartan
- Sparsentan was generally safe and well-tolerated in the double-blind period

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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Baranski, Joel	San Diego, CA	Fornoni, Alessia	Miami, FL	Marder, Brad	Denver, CO	Rheault, Michelle	Minneapolis, MN
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Chaudhuri, Abanti	Palo Alto, CA	Gesualdo, Loreto	Pisa, Italy	Minetti, Enrico	Firenze, Italy	Sanghani, Neil	Nashville, TN
Chorny, Nataliya	New Hyde Park, NY	Gipson, Debbie	Ann Arbor, MI	Mustafa, Esmat	Phoenix, AZ	Sprangers, Ben	Leuven, Belgium
Dell, Katherine	Cleveland, OH	Gibson, Keisha	Chapel Hill, NC	Nester, Carla	Iowa City, IA	Srivastava, Tarak	Kansas City, MO
Derebail, Vimal	Chapel Hill, NC	Haws, Robert	Marshfield, WI	Nelson, Peter	Seattle, WA	Tesar, Vladimir	Prague, Czech Republic
Egidi, Maria	Pisa, Italy	Hogan, Jonathan	Philadelphia, PA	Paredes, Ana	Miami, FL	Woroniecki, Robert	Head of the Harbor, NY
El-Shahawy, Mohamed	Los Angeles, CA	Kopyt, Nelson	Bethlehem, PA	Pergola, Pablo	San Antonio, TX	Zhdanova, Olga	New York, NY