Long-term Effects of Sparsentan, a Dual Angiotensin and Endothelin Receptor Antagonist in Primary Focal Segmental Glomerulosclerosis (FSGS): Interim 84-Week Analysis of the DUET Trial

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Disclosures

- Jonathan Hogan, MD, has received consultancy and advisory board honoraria from Mallinckrodt Pharmaceuticals, Aurinia Pharmaceuticals, Dimerix, Variant Pharmaceuticals, and GSK; and is a co-study principal investigator for the Retrophin, Inc., DUPLEX study
- Vimal K. Derebail, MD, is employed by the University of North Carolina; is a site principal investigator for clinical trials conducted by Retrophin, Inc., Mallinckrodt Pharmaceuticals, Otsuka, ChemoCentryx, Gilead, and InflaRx; and has received honoraria from ASN
- Edward Murphy and Radko Komers, MD, are employees of Retrophin, Inc., and may have an equity or other financial interest in Retrophin, Inc.
- Raguram Parthassarathy, MD, is an advisor and speaker for Mallinckrodt Pharmaceuticals
- Pablo Pergola, MD, PhD, is a site principal investigator for clinical trials conducted by Retrophin, Inc.
- Neil Sanghani, MD, has nothing to disclose
- Howard Trachtman, MD, has received consultancy fees from Kaneka Inc, Otsuka, and ChemoCentryx; and was previously a consultant for Sanofi Genzyme and Optherion, Inc.
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DUET STUDY

Study Objective

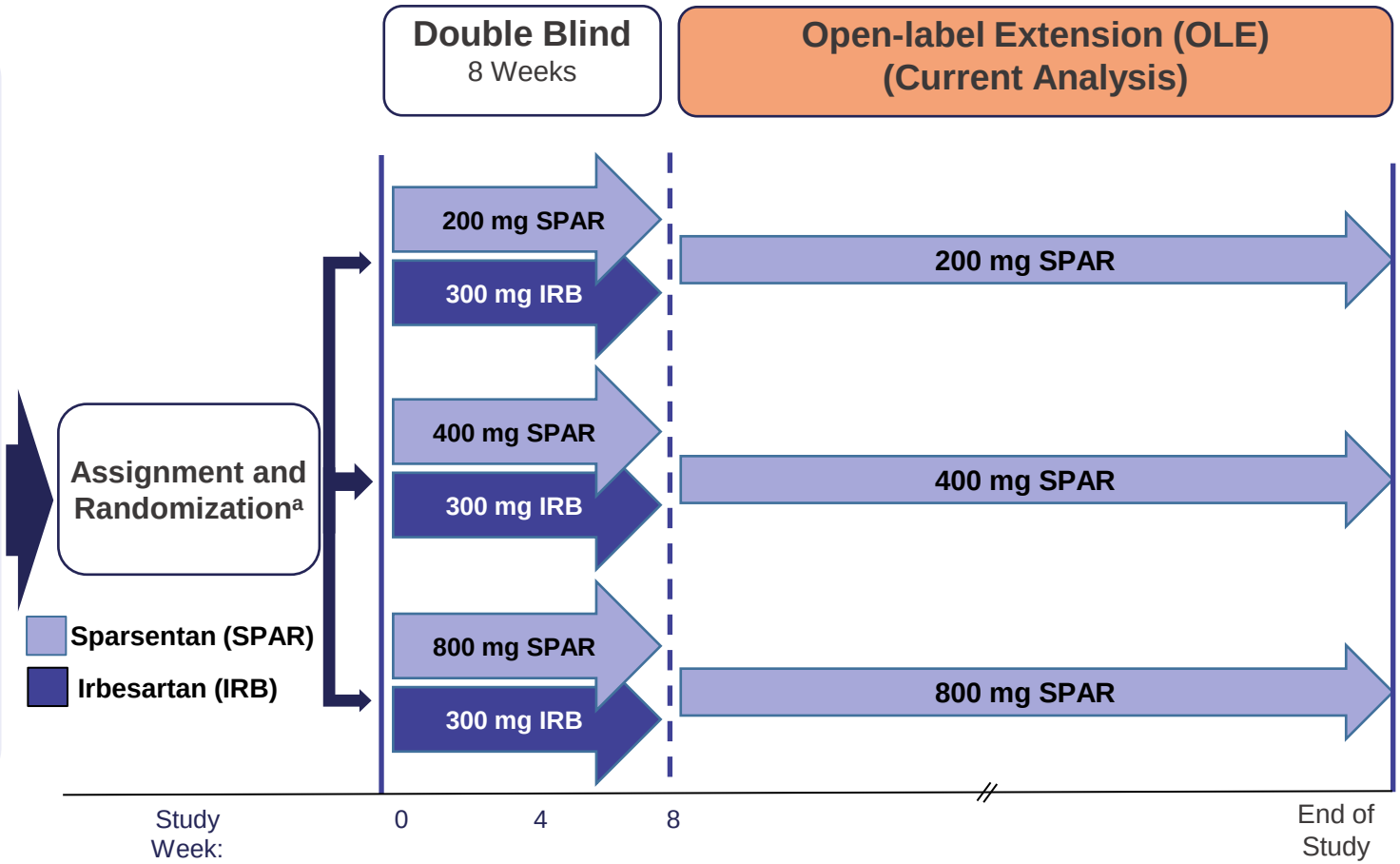
To evaluate the efficacy and safety of sparsentan, as compared with irbesartan, to reduce proteinuria in patients with FSGS during a double-blind study period and an open-label extension

FSGS = focal segmental glomerulosclerosis.

DUET Study Design[1,2]

Selected Criteria

- Patients aged 8–75 (US) or 18–75 (EU) years
- Biopsy-proven FSGS or documented genetic mutation; secondary FSGS excluded
- UP/C ratio ≥1.0 g/g
- eGFR >30 mL/min/1.73 m^2



Note: 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. [a]After 2 weeks' RASI washout. eGFR = estimated glomerular filtration rate; FSGS = focal segmental glomerulosclerosis; RASI = renin-angiotensin system inhibitor; UP/C = urinary protein-to-creatinine ratio.

1. Komers R, et al. *Kidney Int Rep*. 2017;2:654–64. 2. Trachtman H, et al. *J Am Soc Nephrol*. 2018;29(10): DOI: https://doi.org/10.1681/ASN.2018010091

Image adapted from Komers R, et al. *Kidney Int Rep*. 2017;2:654–64.

Study Endpoints

Double-blind Phase

- Primary
  - Percent change in UP/C from baseline to Week 8
- Secondary
  - FSGS partial remission endpoint (FPRE)[1]
    - Proportion of patients who achieved UP/C ≤1.5 g/g and a >40% reduction in UP/C from baseline to Week 8

Open-label Extension

- To determine long-term effects of sparsentan on proteinuria, BP, and eGFR
- To determine long-term safety profile of sparsentan
- Interim analysis at 84 weeks

BP = blood pressure; eGFR = estimated glomerular filtration rate; FSGS = focal segmental glomerulosclerosis; UP/C = urinary protein-to-creatinine ratio .

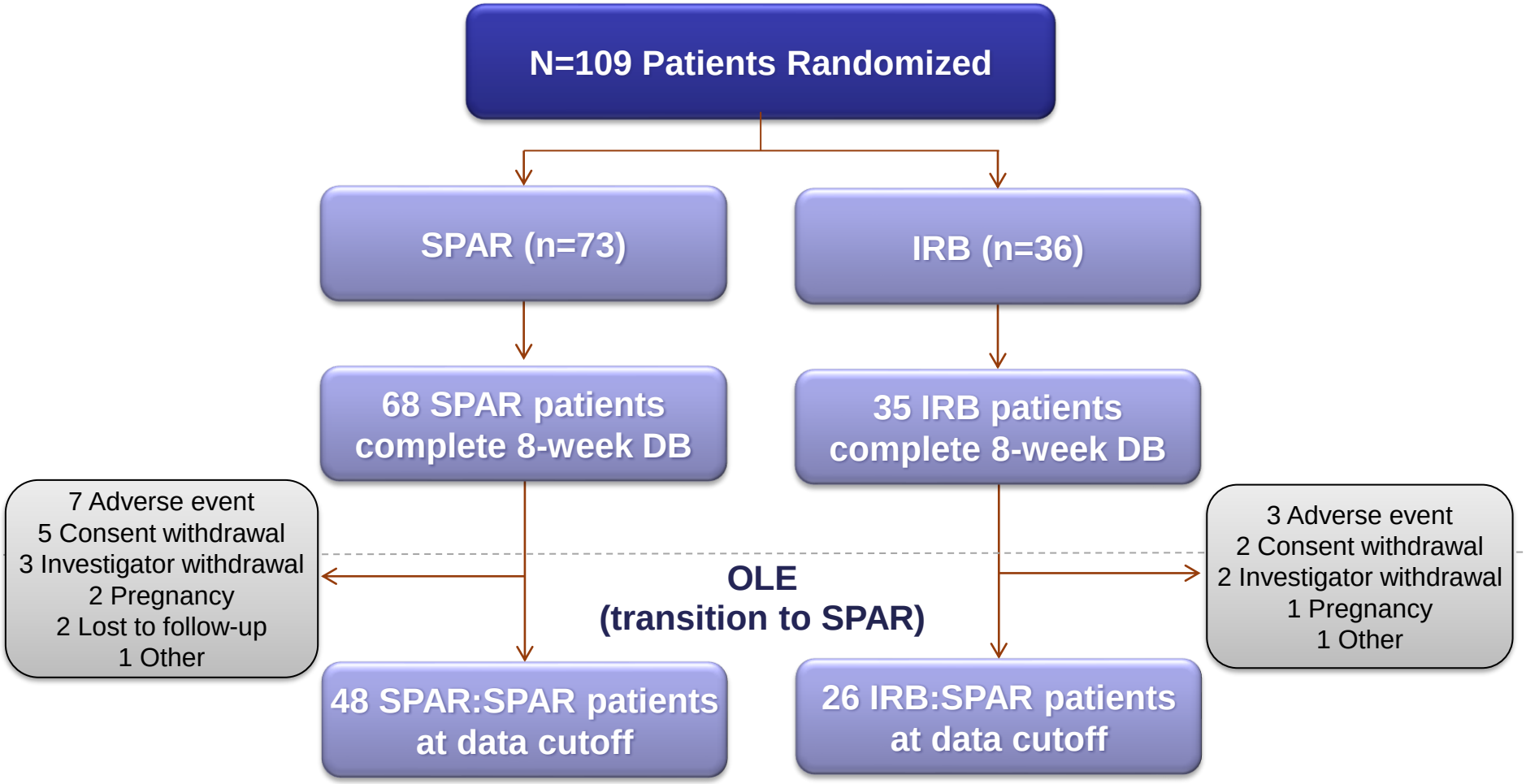
1. Troost JP, et al. *Clin J Am Soc Nephrol*. 2018;13(3):414-21.

Statistical Analysis

- Efficacy analyses included all patients who received open-label SPAR (ie, SPAR:SPAR and IRB:SPAR) and had any efficacy assessments in the OLE
- Safety analyses included all patients who received open-label SPAR (ie, SPAR:SPAR and IRB:SPAR) and had any safety assessments in the OLE
- Baseline was defined as Week 0 for patients receiving SPAR:SPAR and Week 8 for patients receiving IRB:SPAR
- This interim analysis of the OLE included follow-up through 84 weeks

IRB:SPAR = patients randomized to irbesartan who then transitioned to sparsentan in the OLE; OLE = open-label extension; SPAR = sparsentan; SPAR:SPAR = patients randomized to sparsentan who also received sparsentan in the OLE.

Patient Disposition: Interim Data Cutoff[a]



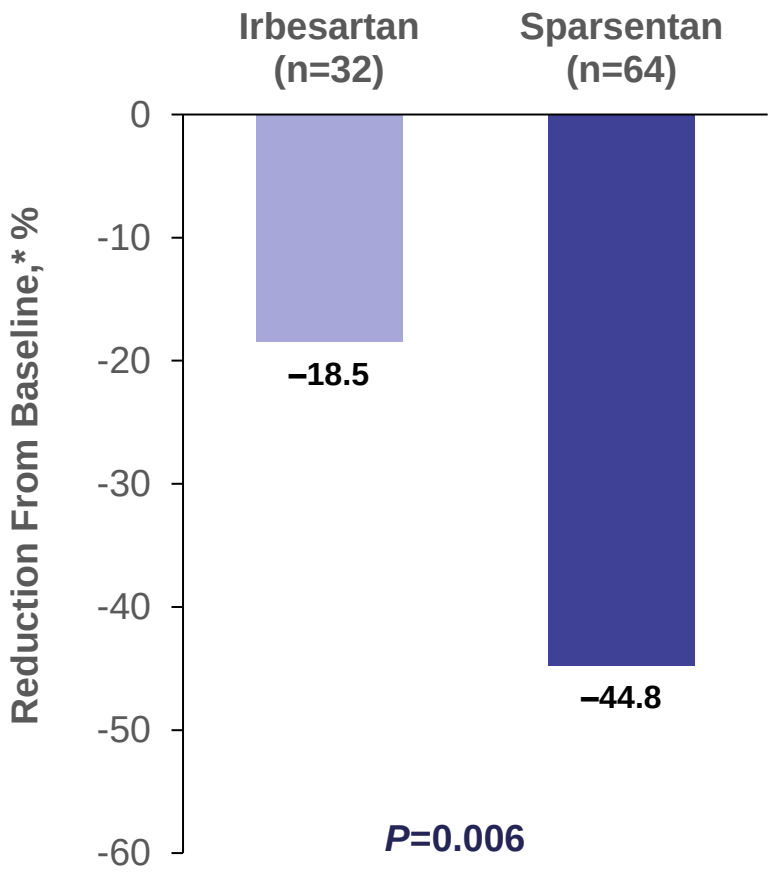
Baseline characteristics of patients transitioning to OLE were similar to those in the DB period

[a]As of November 2017.

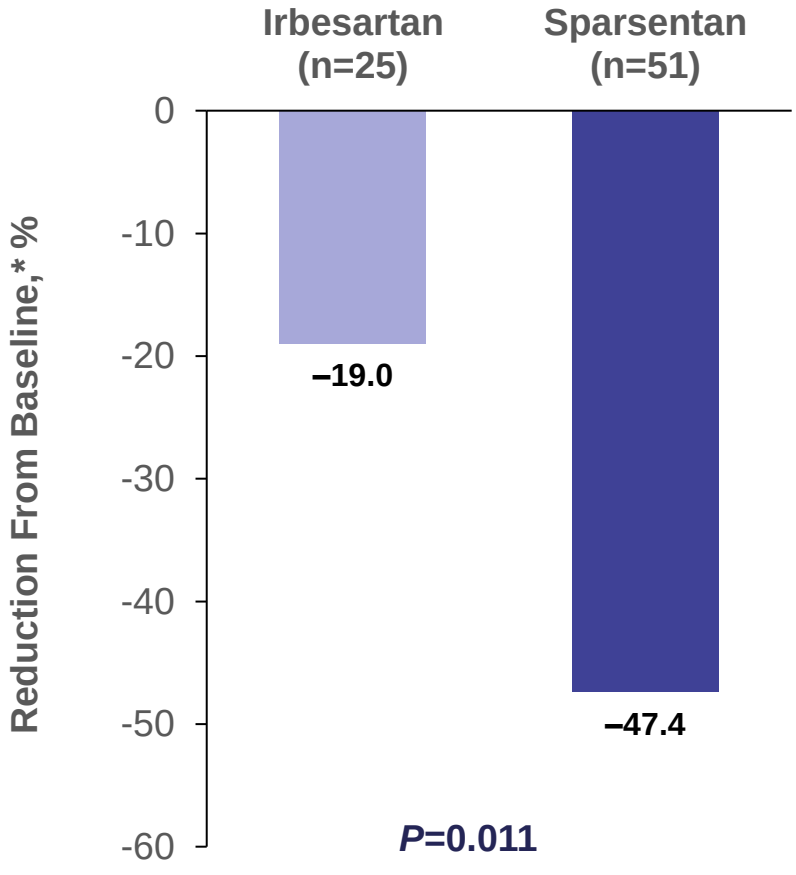
IRB = irbesartan; IRB:SPAR = patients randomized to irbesartan who then transitioned to sparsentan in the OLE; OLE = open-label extension; SPAR = sparsentan; SPAR:SPAR = patients randomized to sparsentan who also received sparsentan in the OLE.

DUET Study: Reduction in UP/C From Baseline to Week 8

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

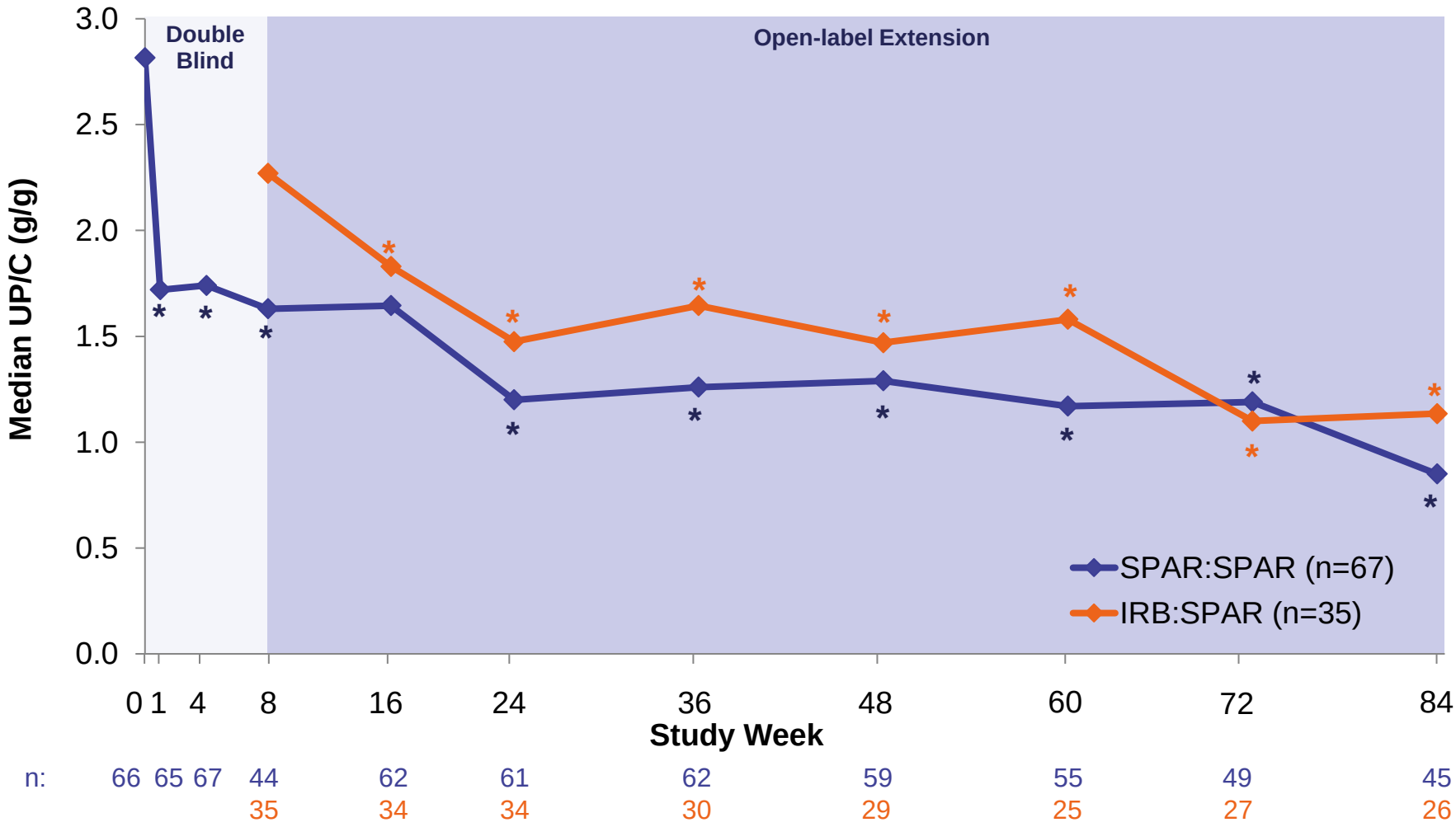


Pooled 400-mg and 800-mg Sparsentan Doses



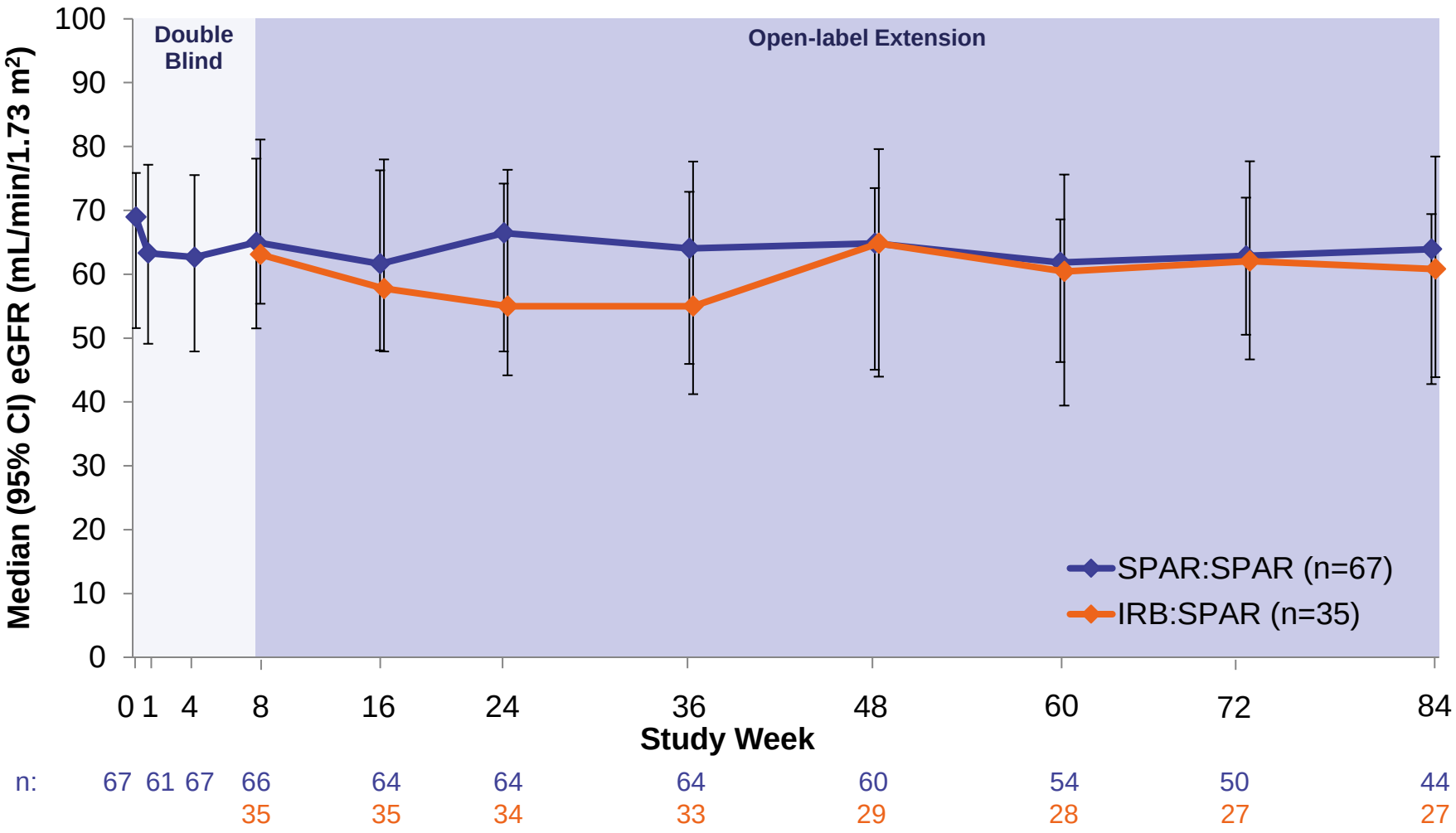
*Geometric least squares mean reduction.
P values from analysis of covariance. Analyses based on the efficacy evaluable set. UP/C based on 24-hour urine.
UP/C = urinary protein-to-creatinine ratio.
Trachtman H, et al. *J Am Soc Nephrol*. 2018;29(10): DOI: https://doi.org/10.1681/ASN.2018010091

Sparsentan Treatment Leads to Sustained Long-term Reduction in Proteinuria



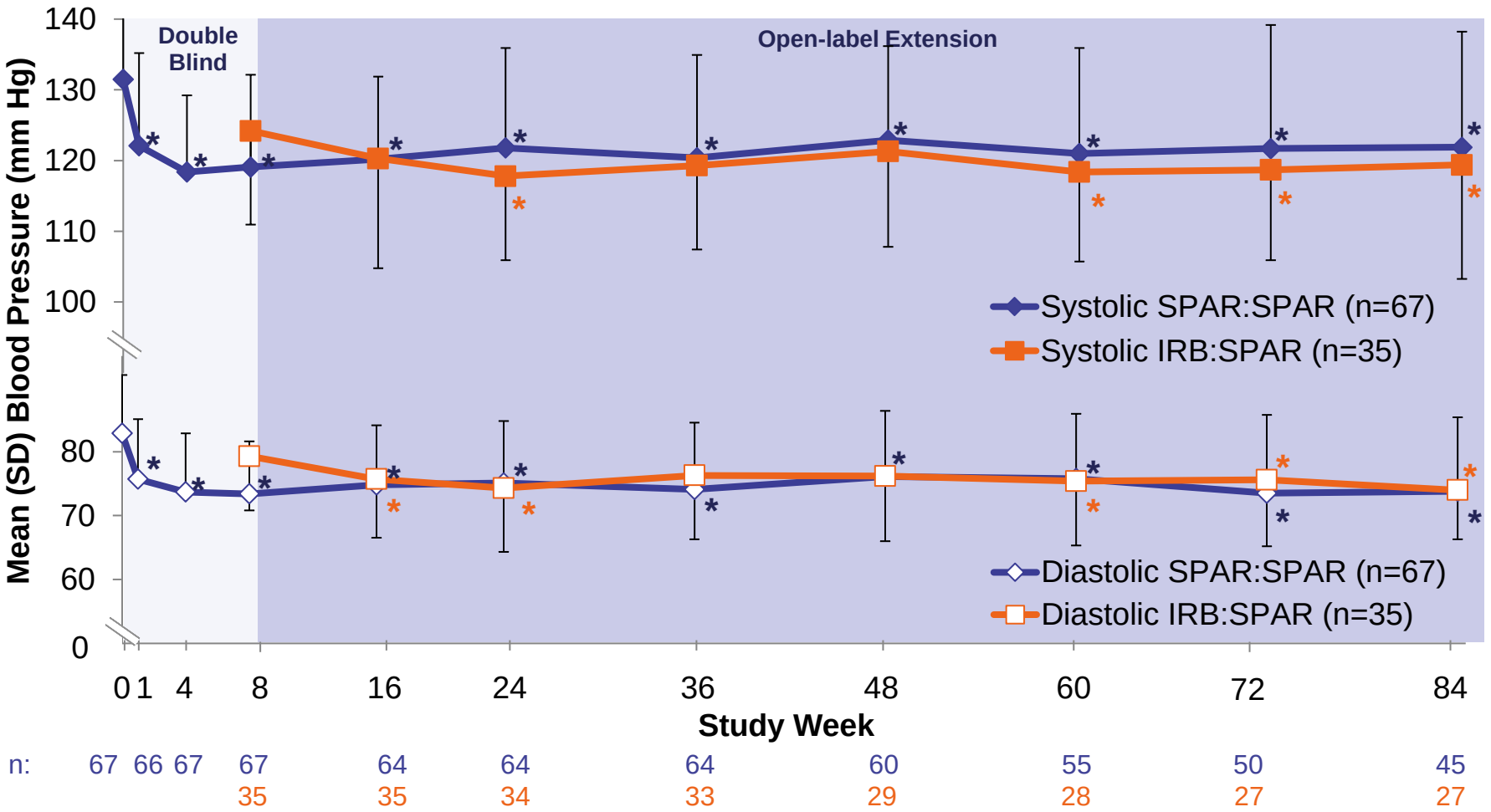
*95% CI of the mean change from baseline (Week 0 for SPAR:SPAR; Week 8 for IRB:SPAR) excludes 0.
Based on the full analysis set. UP/C based on first morning void.
CI = confidence interval; IRB:SPAR = patients randomized to irbesartan who then transitioned to sparsentan in the OLE; OLE = open-label extension; SPAR:SPAR = patients randomized to sparsentan who also received sparsentan in the OLE; UP/C = urinary protein-to-creatinine ratio.

Median eGFR in Sparsentan-treated Patients Over 84 Weeks



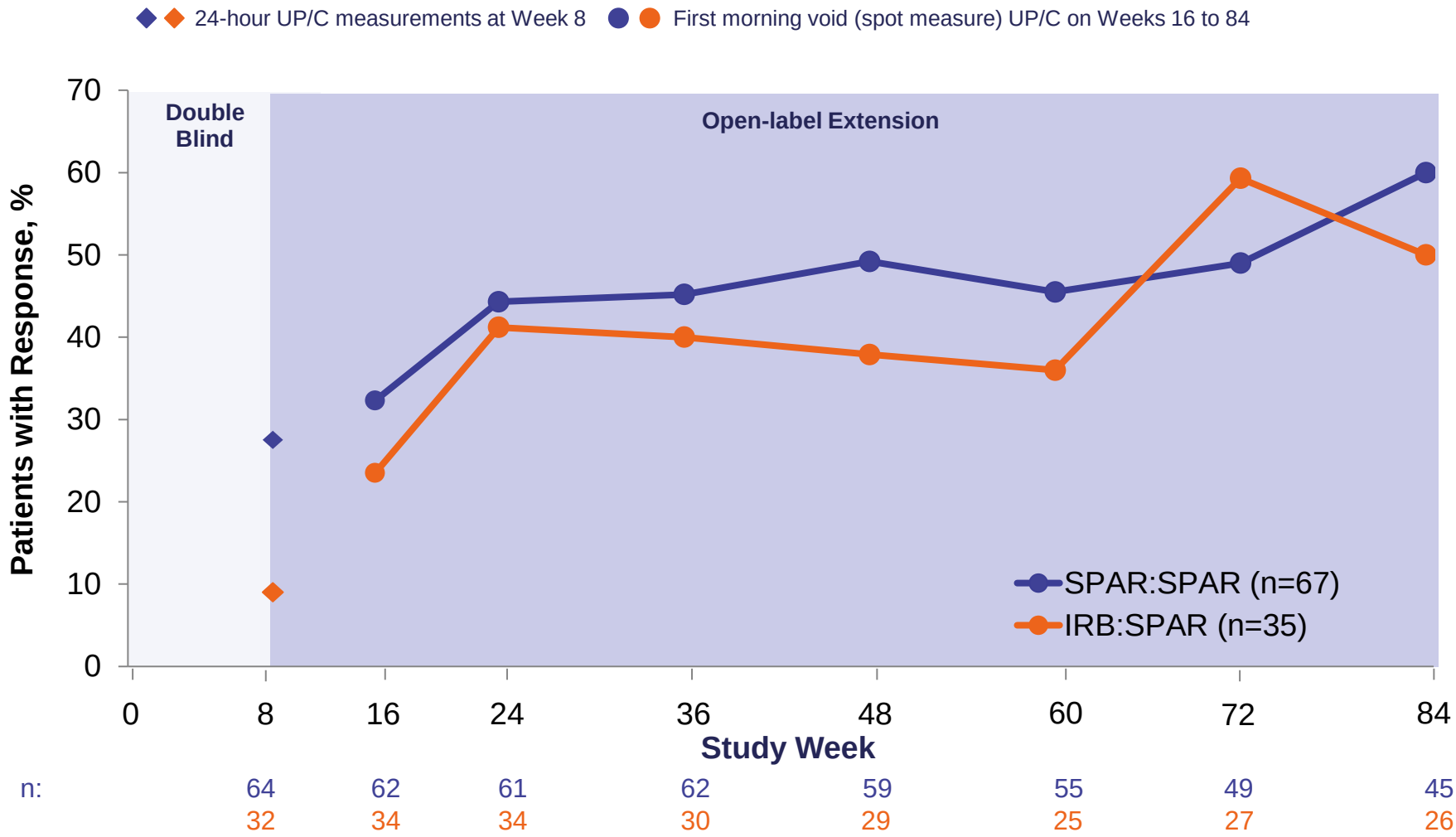
Based on the full analysis set. 95% CIs were calculated for the median value at each time point.
Note: There were 9 study withdrawals due to renal causes during the follow-up period, including 1 case of end-stage renal disease.
CI = confidence interval; eGFR = estimated glomerular filtration rate; IRB:SPAR = patients randomized to irbesartan who then transitioned to sparsentan in the OLE; OLE = open-label extension; SPAR:SPAR = patients randomized to sparsentan who also received sparsentan in the OLE.

Effects of Sparsentan Treatment on Blood Pressure Over 84 Weeks



*95% CI of the mean change from baseline (Week 0 for SPAR:SPAR; Week 8 for IRB:SPAR) excludes 0.
Based on the full analysis set. One-sided error bars represent 1 SD.
BP = blood pressure; CI = confidence interval; IRB:SPAR = patients randomized to irbesartan who then transitioned to sparsentan in the OLE; OLE = open-label extension; SPAR:SPAR = patients randomized to sparsentan who also received sparsentan in the OLE; SD = standard deviation.

Proportion of Patients Achieving UP/C ≤1.5 g/g With >40% UP/C Reduction (FPRE)



FPRE is defined as UP/C ≤1.5 g/g and >40% reduction in UP/C 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). Data for Week 8 is based on the efficacy evaluable set. Data for Weeks 16 to 84 are based on the full analysis set.

FPRE = FSGS partial remission endpoint; FSGS = focal segmental glomerulosclerosis; IRB:SPAR = patients randomized to irbesartan who then transitioned to sparsentan in the OLE; OLE = open-label extension; SPAR:SPAR = patients randomized to sparsentan who also received sparsentan in the OLE; UP/C = urinary protein-to-creatinine ratio.

TEAEs During Treatment With Sparsentan for Subjects Who Entered OLE[a]

	Patients with TEAEs	
	SPAR:SPAR (n=67)	IRB:SPAR[b] (n=35)
Patients with ≥1 TEAE, n (%)	63 (94.0)	32 (91.4)
TEAEs Occurring in ≥10%, n (%)		
Headache	20 (29.9)	6 (17.1)
Edema, peripheral	16 (23.9)	5 (14.3)
Hypotension	15 (22.4)	3 (8.6)
Nausea	13 (19.4)	0 (0.0)
Dizziness	12 (17.9)	2 (5.7)
Anemia[c]	10 (14.9)	6 (17.2)
Diarrhea	10 (14.9)	3 (8.6)
Hypertension	5 (7.5)	5 (14.3)
Sinusitis	3 (4.5)	5 (14.3)
Cough	9 (13.4)	2 (5.7)
Hyperkalemia	9 (13.4)	2 (5.7)
Pyrexia	9 (13.4)	1 (2.9)
Vomiting	9 (13.4)	1 (2.9)
Blood creatinine increased	7 (10.4)	3 (8.6)
Fatigue	7 (10.4)	0 (0.0)
Nasal congestion	7 (10.4)	3 (8.6)
Nasopharyngitis	7 (10.4)	2 (5.7)
Oropharyngeal pain	7 (10.4)	1 (2.9)
Upper respiratory tract infection	7 (10.4)	5 (14.3)
Patients with ≥1 serious TEAE, n (%)	19 (28.4)	7 (20.0)

[a]Total duration of sparsentan exposure in patients who entered the OLE was 124.5 patient-years for SPAR:SPAR and 61.1 patient-years for IRB:SPAR.
[b]Does not include TEAEs reported during 8 weeks of double-blind treatment with irbesartan.
[c]Includes anemia, iron-deficiency anemia, and decreased blood hemoglobin.
OLE, open-label extension; TEAEs, treatment-emergent adverse events.

Conclusions

- In the DUET OLE, sparsentan achieved sustained decrease in proteinuria and blood pressure over 84 weeks in patients with FSGS
  - This occurred in patients who received either sparsentan or irbesartan in the initial 8-week double-blind period of the study
- An increasing proportion of patients achieved FPRE with ongoing sparsentan treatment in the OLE
  - FPRE is defined as UP/C ≤1.5 g/g and >40% reduction in UP/C from baseline
- Sparsentan was well tolerated during the OLE
- Overall, these findings suggest that sparsentan has long-term nephroprotective potential
- The ongoing phase 3 DUPLEX study will further characterize the long-term antiproteinuric efficacy and nephroprotective potential, as well as the safety profile, of sparsentan in FSGS

FPRE = FSGS partial remission endpoint; FSGS = focal segmental glomerulosclerosis; OLE = open-label extension; UP/C = urinary protein-to-creatinine ratio.

Thank You to the DUET Physicians, Coordinators, and Patients

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Elliott, Matthew	Charlotte, NC	Kopyt, Nelson	Bethlehem, PA	Pergola, Pablo	San Antonio, TX	Zhdanova, Olga	New York, NY