Long-Term Effect of Sparsentan (SPAR), a Dual Angiotensin and Endothelin Receptor Antagonist, on Proteinuria in Patients with Primary FSGS: Interim Analysis of the DUET Trial

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Disclosures

Howard Trachtman, MD	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.
Ivan Rychlik, MD, PhD	Author declares there are no competing interests.
Robert Haws, MD	Author declares there are no competing interests.
Carla Nester, MD	Author declares there are no competing interests.
Alessia Fornoni, MD, PhD	Vice President and CSO, L&F Health LLC. L&F Health LLC and affiliated companies have a patent estate covering topics relevant to FSGS. L&F Health LLC has consulting agreements with and/or has received honoraria from Hoffman La Roche, Genentech, Mesoblast, Bristol Myers Squibb, Abbvie, Jenssen, Boehringer Ingelheim, Astra Zeneca, Pfizer, Chemocentryx, Dimerix, Mallinckrodt, and Variant Pharmaceuticals. Variant Pharmaceuticals has licensed worldwide rights to develop and commercialize hydroxypropyl beta cyclodextrin for treatment of kidney disease from L&F Research.
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DUET STUDY

Study Objective:

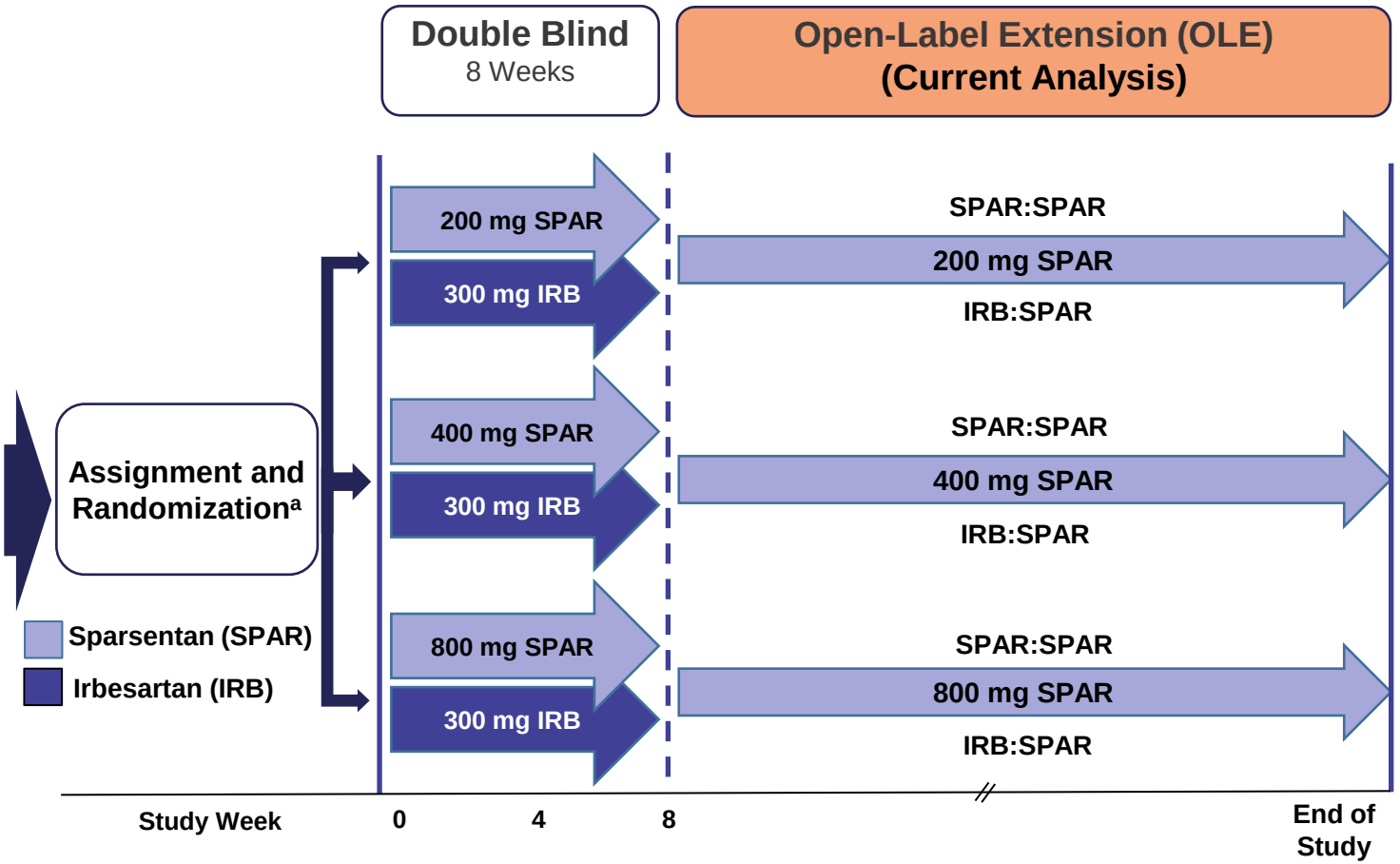
To evaluate the efficacy and safety of sparsentan, as compared with irbesartan, to reduce proteinuria in patients with primary FSGS during an 8-week, double-blind study period and an open-label extension

FSGS = focal segmental glomerulosclerosis.

DUET Study Design

Selected Criteria

- Patients aged 8–75 (US) or 18–75 (EU) years
- Biopsy-proven primary FSGS or documented genetic mutation; patients with secondary FSGS were excluded
- UPC 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; IRB:SPAR = patients randomized to irbesartan who then transitioned to sparsentan in the OLE; RASI = renin-angiotensin system inhibitor; SPAR:SPAR = patients randomized to sparsentan who also received sparsentan in the OLE; UPC = urinary protein-to-creatinine ratio.

Study Endpoints

Double Blind

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

Open-Label Extension

- To determine the effect of sparsentan on UPC, BP, and eGFR over time (interim analysis through 48 weeks)
- To determine the safety profile of sparsentan over time (interim analysis through 48 weeks)

1. Troost JP, et al. *Clin J Am Soc Nephrol*. In press.

Statistical Analysis

- Efficacy analyses include all patients who receive open-label SPAR (ie, SPAR:SPAR and IRB:SPAR) and have any efficacy assessment in the OLE
- Safety analyses include all patients who receive open-label SPAR (ie, SPAR:SPAR and IRB:SPAR) and have any safety assessment 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 48 weeks

DUET: Results from 8-Week Double-Blind Period

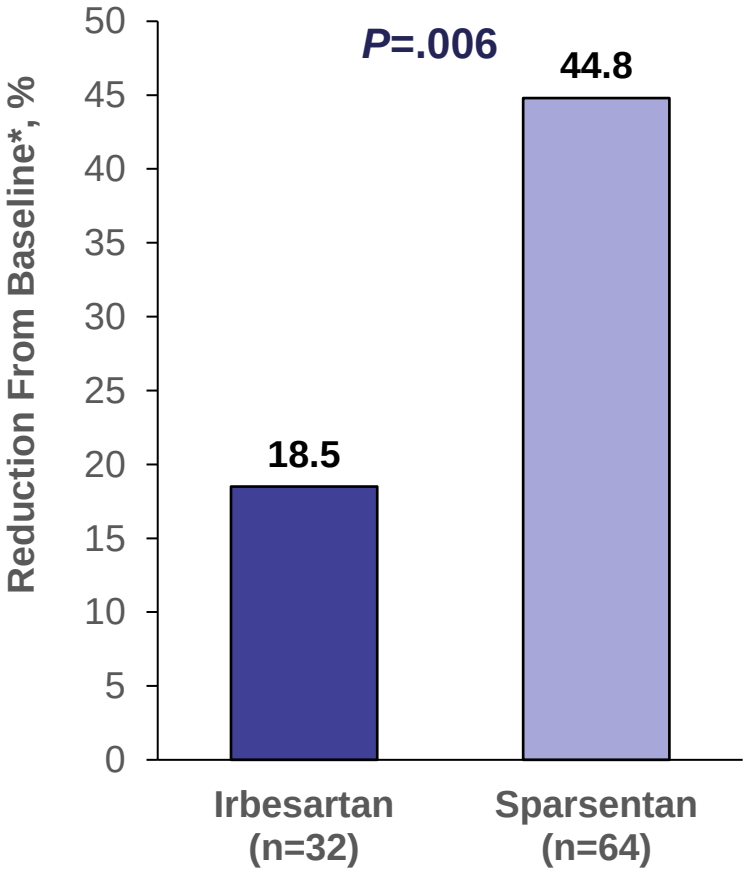
Baseline Characteristics

	Irbesartan (n=32)	Sparsentan, all doses (n=64)
Age, n (%), years		
Pediatric (8–18 years)	8 (25)	12 (19)
Adult (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 (6.1)
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)

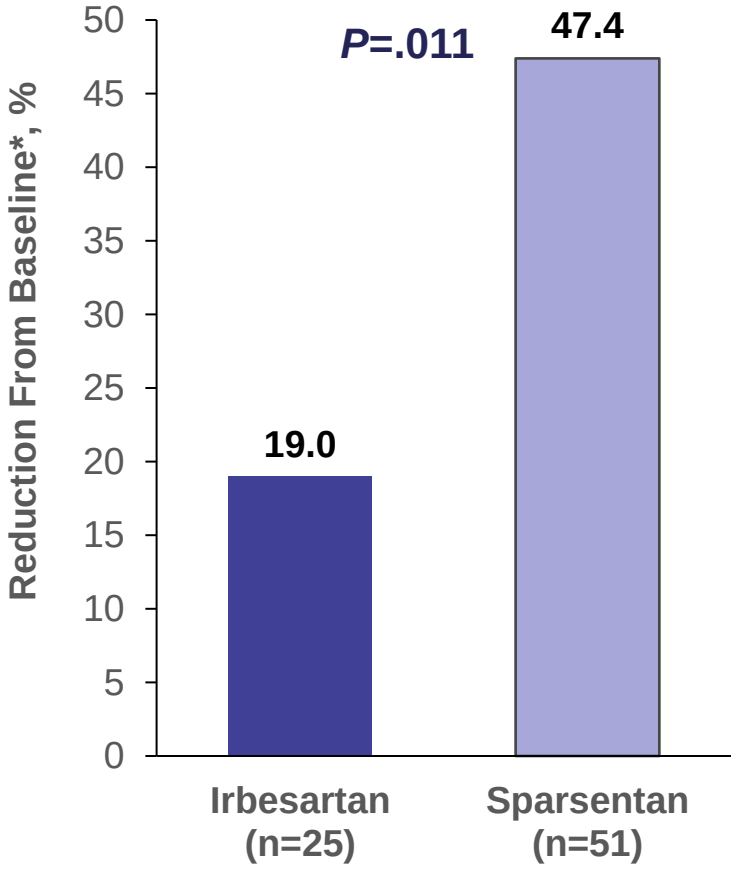
ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; eGFR = estimated glomerular filtration rate; SD = standard deviation; UPC = urinary protein-to-creatinine ratio.

DUET Study – Reduction in UPC from Baseline to Week 8

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



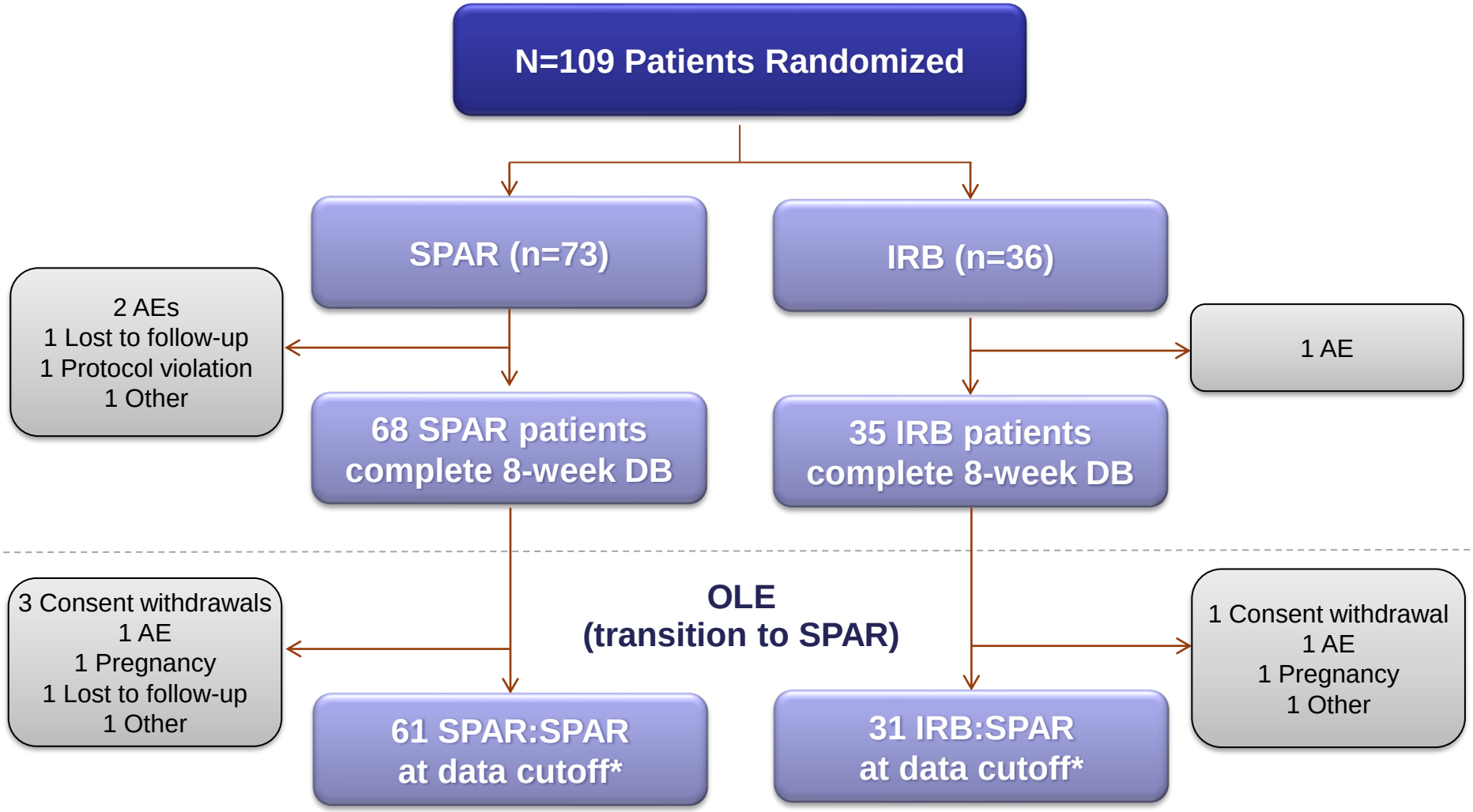
Pooled 400-mg and 800-mg Sparsentan Doses



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

DUET OLE: Patient Disposition

Patient Disposition – Interim Data Cutoff

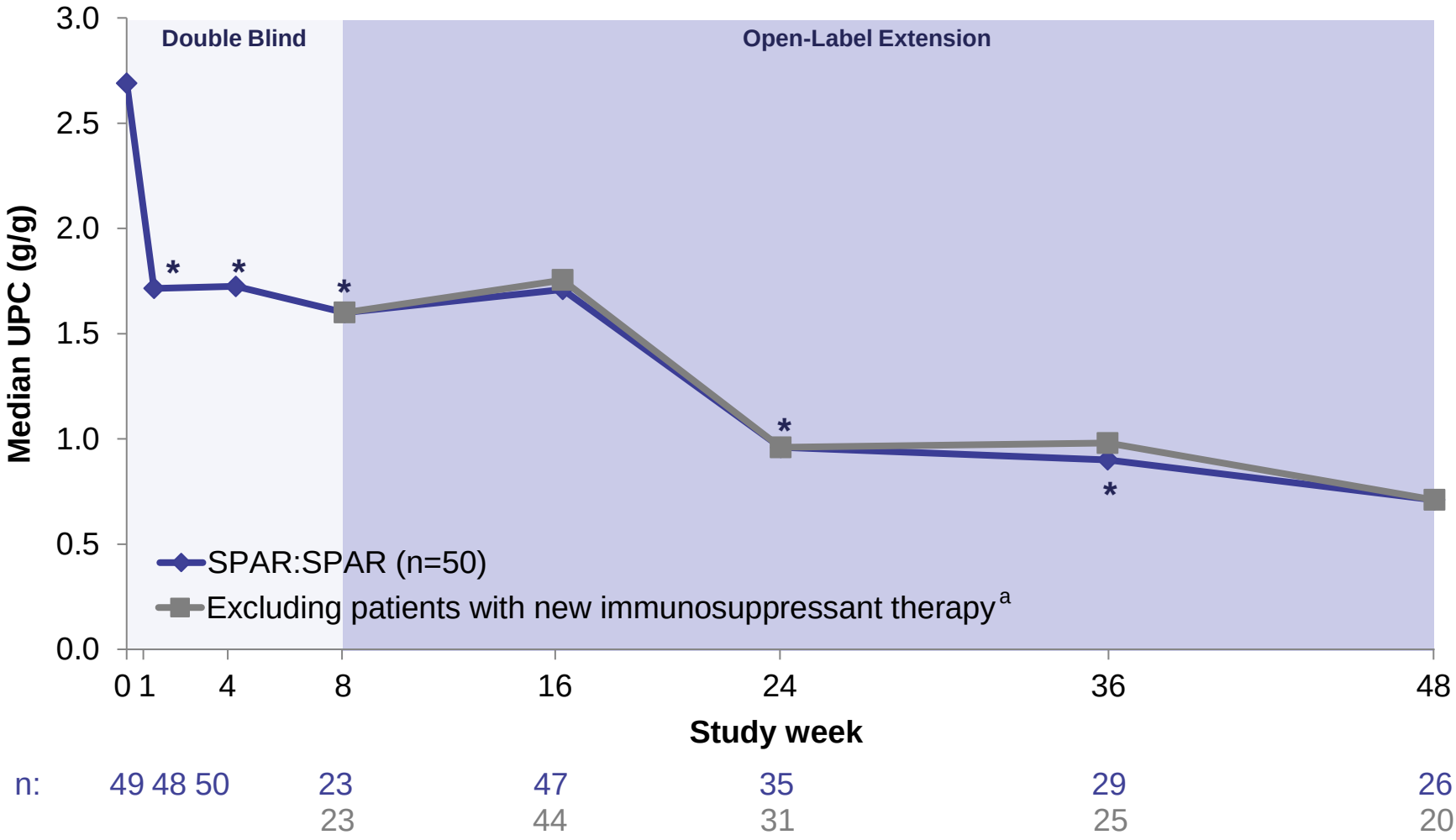


Baseline characteristics of patients in the OLE were similar to those in the DB period

*As of June 9, 2016.

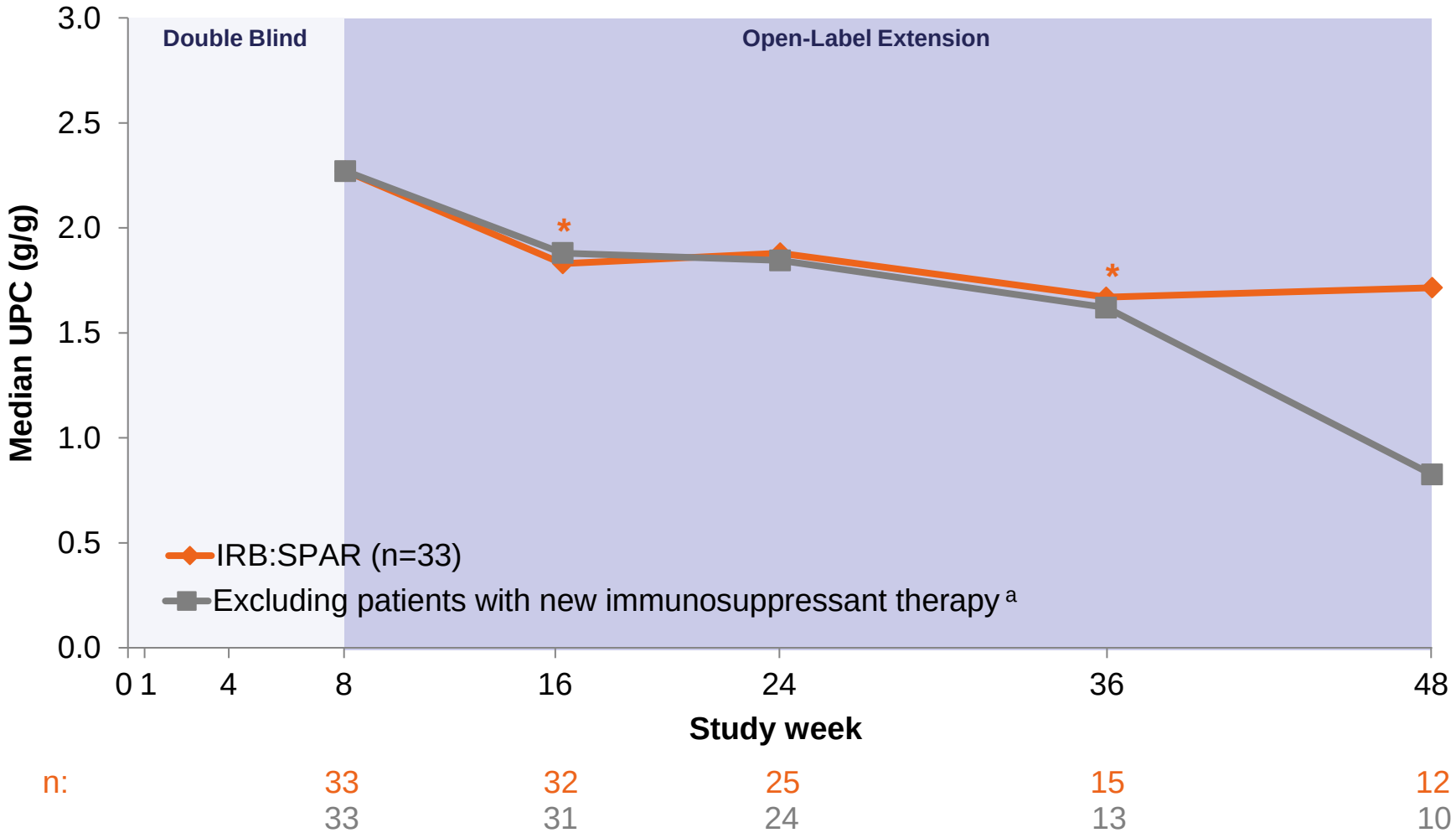
DUET OLE: Interim Efficacy and Safety Analysis

Reduction in UPC Over 48 Weeks (SPAR:SPAR)



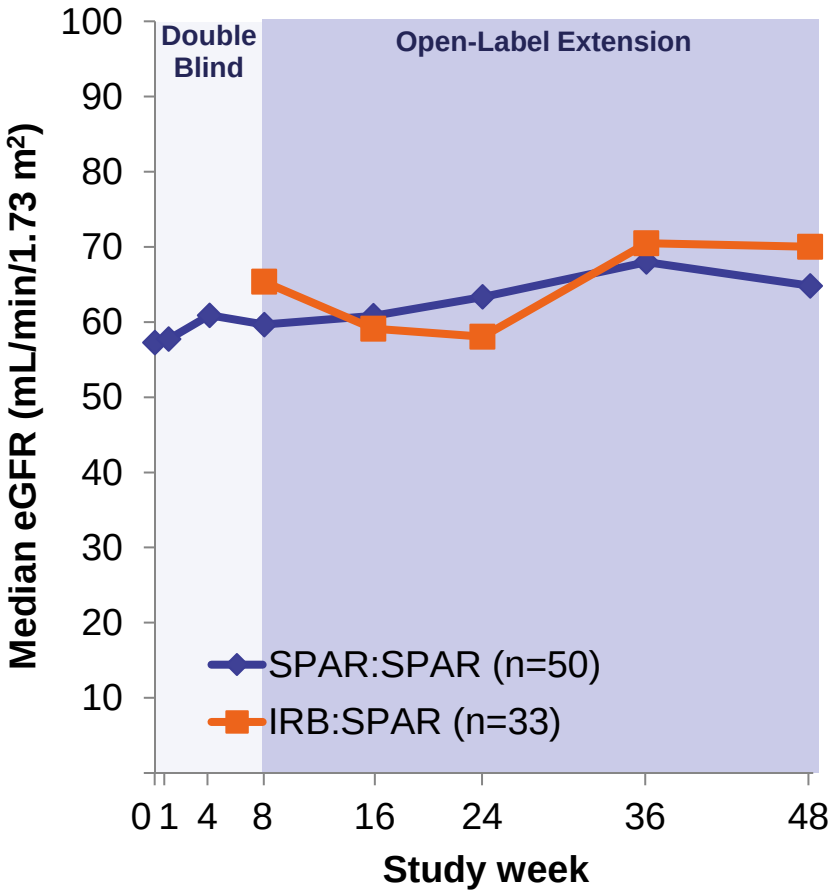
*P<.05 for mean change from baseline (week 0).
[a]Data were truncated after the start of new immunosuppressant treatments in the OLE.

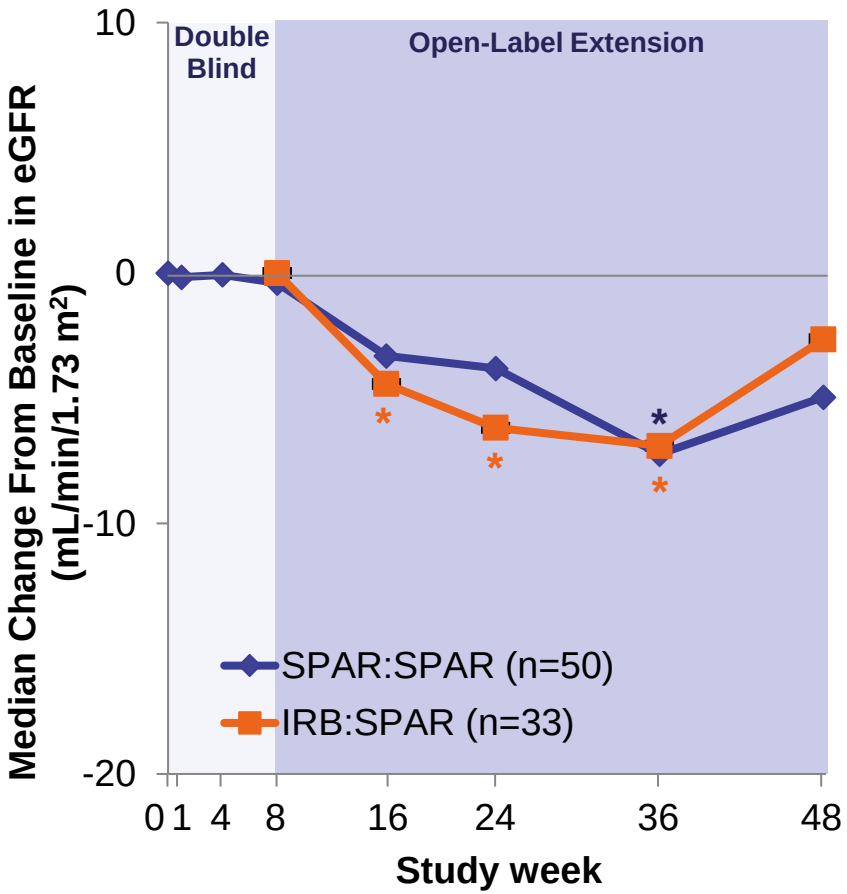
Reduction in UPC Over 48 Weeks (IRB:SPAR)



*P<.05 for mean change from baseline (week 8).
[a]Data were truncated after the start of new immunosuppressant treatments in the OLE.

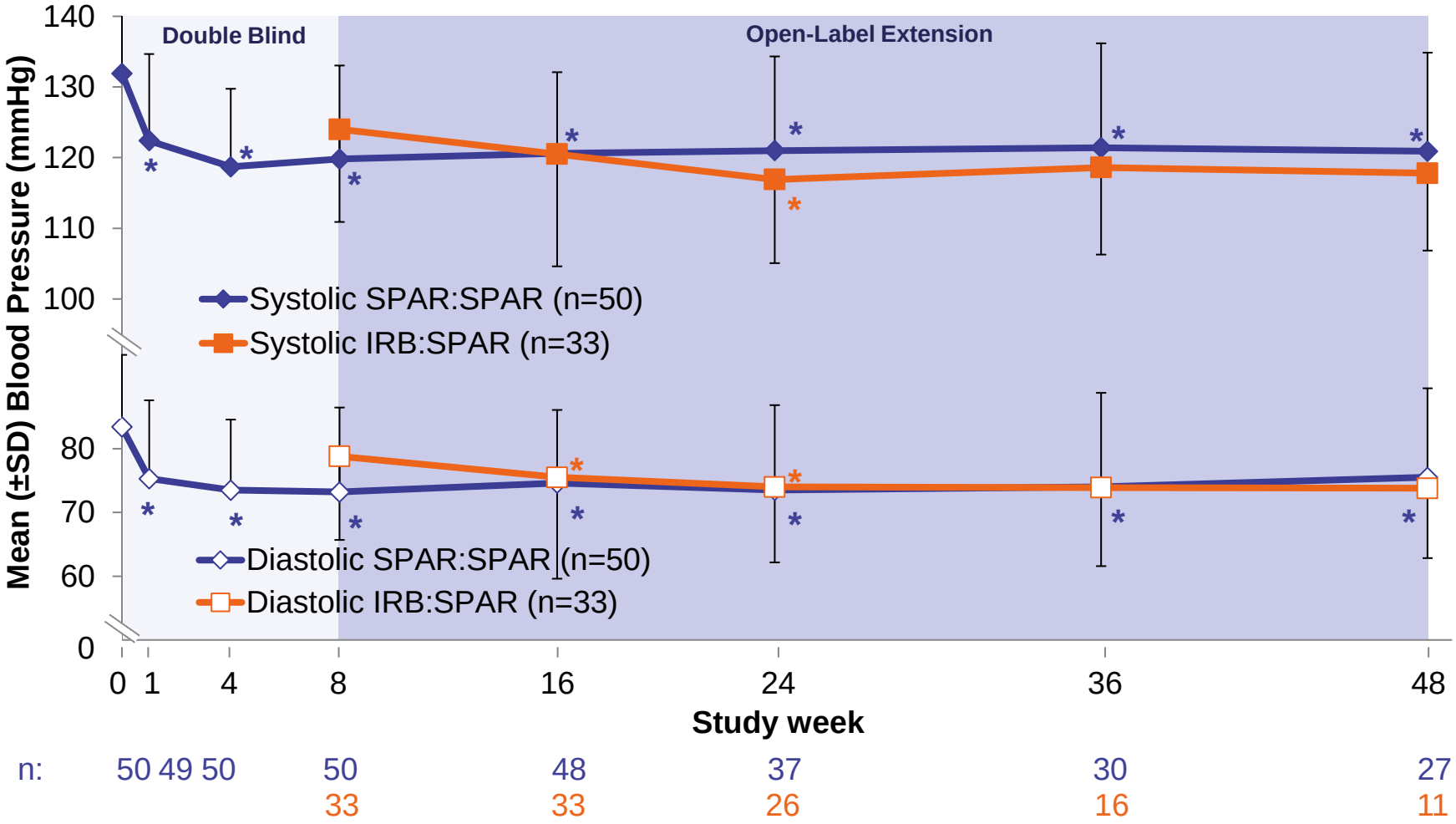
eGFR Remained Stable Over 48 Weeks





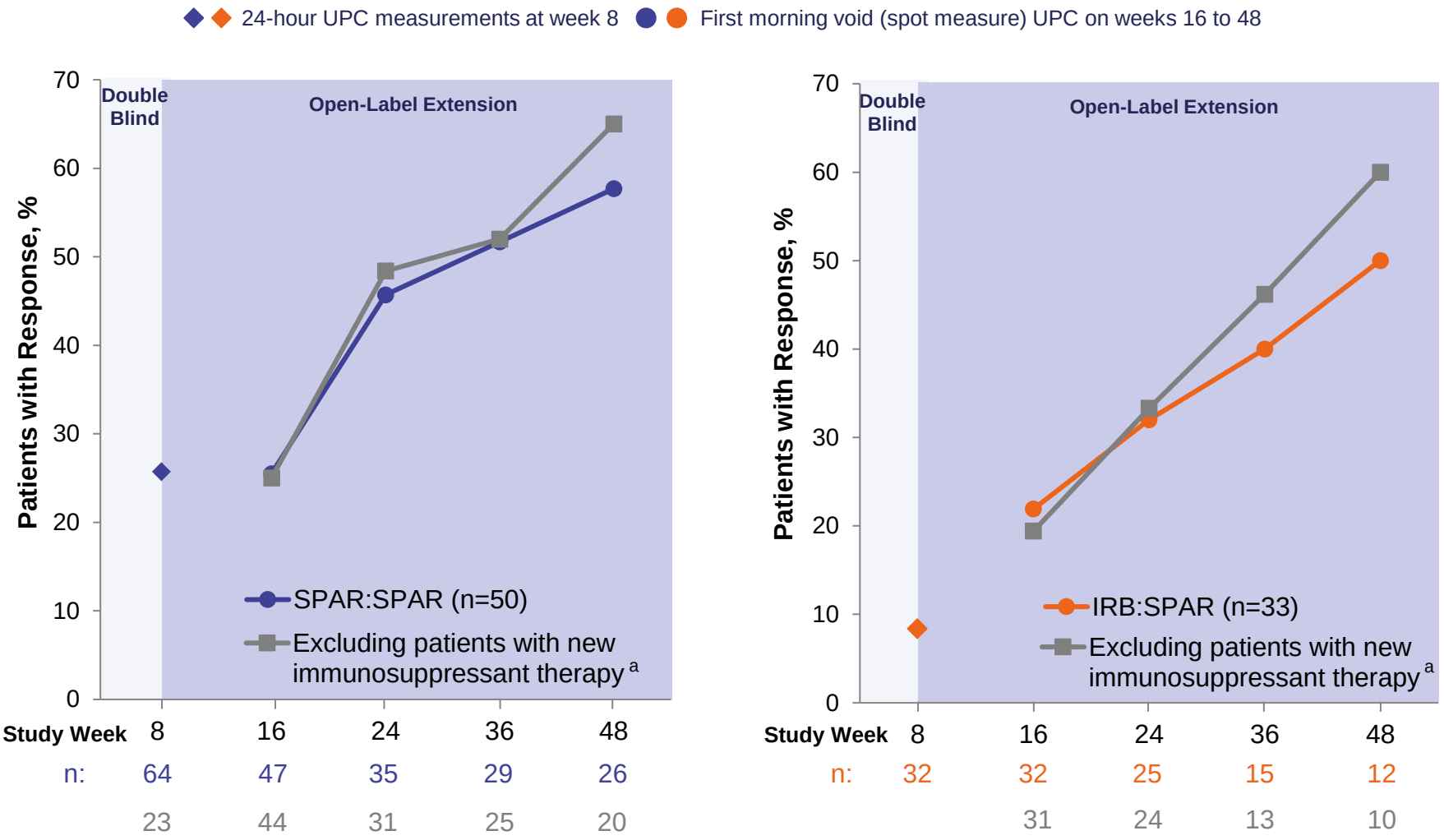
**P*<.05 for mean change from baseline (week 0 for SPAR:SPAR and week 8 for IRB:SPAR).

Effects of SPAR on Blood Pressure



*P<.05 vs. baseline (week 0 for SPAR:SPAR and week 8 for IRB:SPAR).

Modified Partial Remission During the Open-Label Extension



[a]Data were truncated after the start of new immunosuppressant treatments in the OLE.
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.

Treatment-Emergent Adverse Events (TEAEs)

	Patients with TEAEs from Baseline N (%)	
	SPAR:SPAR (n=57)	IRB:SPAR (n=33)
Patients with ≥1 serious TEAE, n (%)	7 (12.3)	3 (9.1)
Patients with ≥1 TEAE, n (%)	51 (89.5)	24 (72.7)
TEAEs Occurring in ≥10%, n (%)		
Anemia[a]	9 (15.8)	5 (15.2)
Cough	6 (10.5)	2 (6.1)
Diarrhea	7 (12.3)	2 (6.1)
Dizziness	11 (19.3)	2 (6.1)
Edema	6 (10.5)	0
Edema, peripheral	9 (15.8)	1 (3.0)
Headache	15 (26.3)	5 (15.2)
Hypotension	9 (15.8)	2 (6.1)
Nausea	11 (19.3)	0
Upper respiratory tract infection	5 (8.8)	4 (12.1)

[a]Includes anemia, iron-deficiency anemia, and decreased blood hemoglobin.

Strengths and Limitations

Strengths

- High rate of rollover into the OLE
- Limited drop-out
- Collection of patient-reported outcomes data

Limitations

- No washout
- No direct measurement of GFR
- Lack of measures of changes in renin-angiotensin axis or endothelin

Conclusions

- Patients with primary FSGS achieved progressive reduction in proteinuria with SPAR over 48 weeks in the DUET study OLE
  - SPAR effects on proteinuria were associated with stable eGFR
  - After reduction at early time points, BP remained stable during the OLE
- Transition to SPAR from IRB led to further reduction in proteinuria with long-term stability in eGFR
- Effects of SPAR were similar, even after exclusion of data following new immunosuppressant therapy during the OLE
- SPAR was well tolerated during the OLE, including in patients who transitioned from IRB
- 74 patients remain in the OLE
- A future Phase 3 study will further characterize long-term effects of SPAR on preservation of kidney function and proteinuria in primary FSGS

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