Complete Remission of Proteinuria in Patients with Focal Segmental Glomerulosclerosis (FSGS) Treated with Sparsentan, a Dual Endothelin and Angiotensin Receptor Antagonist, in the DUET Trial: A Post-hoc Analysis

Jonathan Hogan[1], Ulysses Diva[2], Edward Murphy[2], Noah Rosenberg[2], Howard Trachtman[3] and Radko Komers[4]
on behalf of the DUET Study Group

[1]Division of Nephrology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [2]Research & Development, Retrophin, Inc., San Diego, CA; [3]Division of Pediatric Nephrology, New York University School of Medicine, Langone Medical Center, New York, NY; [4]Nephrology, Retrophin, Inc., San Diego, CA

Disclosures

- Jonathan Hogan, MD, has received consultancy and advisory board honoraria from Retrophin, Inc., Mallinckrodt, Aurinia Pharmaceuticals, Zyversa (Variant) Pharmaceuticals, Goldfinch Bio, Dimerix, GSK, Calliditas and Alexion. He has received salary support as site principal investigator for studies sponsored by Retrophin, Inc., BMS, Calliditas, Gilead, Boehringer Ingelheim, GSK, Regeneron, Achillion (Alexion), Complexa, Omeros, and the National Institutes of Health. He is also a site principal investigator for the DUET and DUPLEX studies.
- Ulysses Diva, PhD, Edward Murphy, Noah Rosenberg, MD, and Radko Komers, MD, PhD, are employees of Retrophin, Inc., and may have an equity or other financial interest in Retrophin, Inc.
- Howard Trachtman, MD, has received consultancy fees from ChemoCentryx, Kaneka, and Otsuka; and was previously a consultant to Genzyme and Optherion. He has consultancy agreements with Goldfinch Biopharma and Retrophin, Inc. through NYU.
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Background

- The **goal of therapy in FSGS** is to induce a **complete or partial remission of proteinuria**[1,2] as they are **both strong predictors of kidney survival**[3]
- The novel modified FSGS partial remission endpoint (**FPRE: UP/C <1.5 g/g and >40% reduction in proteinuria from baseline**) also is a strong predictor of long-term kidney outcomes[3]
- The **DUET study examined the antiproteinuric effect of sparsentan**, the dual-acting selective antagonist of the endothelin type A receptor and the angiotensin II AT1 receptor, in patients with FSGS[4]
  - Treatment with **sparsentan** (200 to 800 mg/day, pooled) resulted in a **greater reduction of proteinuria** compared with irbesartan over the 8-week double-blind period[4]
  - FPRE was examined at the end of the double-blind period and in the open-label extension (OLE)
    - At **8 weeks,** FPRE was achieved in **28% of sparsentan-treated** and **9% of irbesartan-treated patients** (P=0.04)[4]
    - At **84 weeks** in the OLE, **56% of patients** receiving sparsentan **achieved FPRE**[5]
- The proportion of patients achieving complete remission of proteinuria has not been examined in the DUET OLE

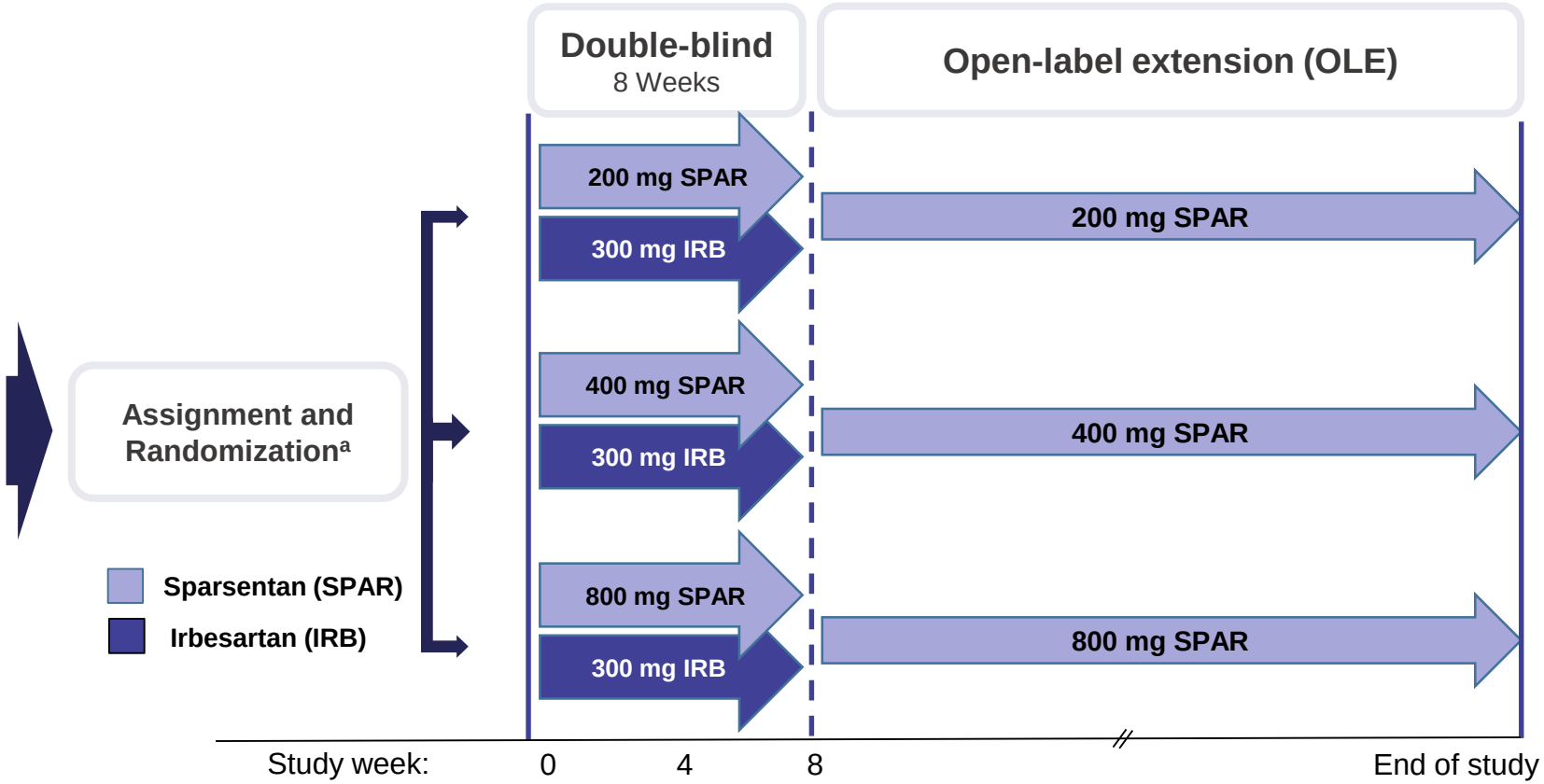
1. D'Agati VD, et al. *N Engl J Med.* 2011;365:2398-411; 2. KDIGO Clinical Practice Guideline for Glomerulonephritis. Public review draft (June 2020); 3. Troost JP, et al. *Clin J Am Soc Nephrol*. 2018;13:414-21; 4. Trachtman H, et al. *J Am Soc Nephrol*. 2018;29:2745-54; 5. Hogan J, et al. Presented at American Society of Nephrology Kidney Week, October 23-28, 2018, San Diego, CA.

DUET: Multicenter, Randomized, Active-Control Study With OLE[1,2]

- **AIM of the current DUET post-hoc analysis:**
  - To identify the proportion and characteristics of patients treated with sparsentan who achieved complete remission (normalization) of proteinuria

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: 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 of RASI washout. eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; RASI, renin-angiotensin system inhibitor; UP/C, urinary protein-to-creatinine ratio. DUET trial NCT01613118.

1. Komers R, et al. *Kidney Int Rep*; 2017;2:654-64; 2. Trachtman H, et al. *J Am Soc Nephrol*. 2018;29:2745-54.

Methods

- **Patients treated with sparsentan were included** in this post-hoc analysis of DUET
  - Randomized to sparsentan in the double-blind period and continued sparsentan in the OLE
  - Randomized originally to irbesartan in the double-blind period and transitioned to sparsentan in the OLE
- **UP/C and eGFR were measured every 12 weeks** during the OLE
- **Complete remission** (normalization) of proteinuria was defined as first morning void UP/C ≤0.3 g/g at any post-baseline visit while on sparsentan
- **Sustainability of complete remission** of proteinuria was determined for patients with at least 2 consecutive UP/C ≤0.3 g/g and derived as the total duration beginning from UP/C ≤0.3 g/g and ending when UP/C >0.6 g/g
- **Slope of eGFR** was determined via a mixed-effects model with linear spline (ie, a 2-slope model with knot or change point at Week 6) including a fixed effect for baseline eGFR and random effects for intercept and slope terms

Baseline Demographic Characteristics of Patients Who Did and Did Not Achieve UP/C ≤0.3 g/g At Any Visit While on Sparsentan

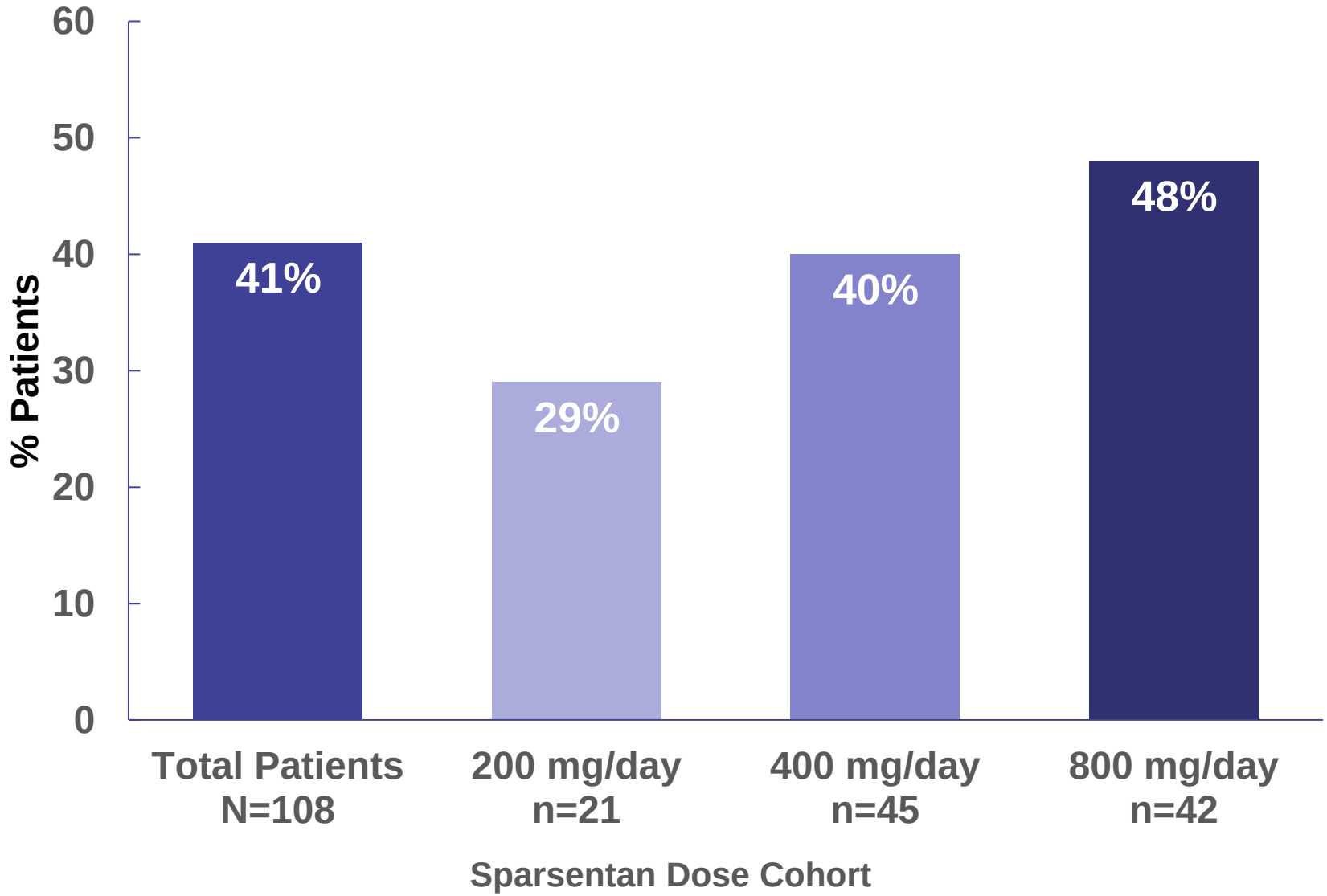
	Any UP/C ≤0.3 g/g (n=44)	No UP/C ≤0.3 g/g (n=64)
Age, mean (SD) / median	38.3 (17.69) / 39.0	35.9 (15.73) / 37.5
Age <18 years, n (%)	8 (18.2)	10 (15.6)
Sex		
Female, n (%)	18 (40.9)	30 (46.9)
Male, n (%)	26 (59.1)	34 (53.1)
Ethnicity, n (%)		
Hispanic/Latino	7 (15.9)	12 (18.8)
Race, n (%)		
Asian	2 (4.5)	4 (6.3)
Black	7 (15.9)	8 (12.5)
White	33 (75.0)	49 (76.6)
Other	2 (4.5)	3 (4.7)

Baseline Clinical Characteristics of Patients Who Did and Did Not Achieve UP/C ≤0.3 g/g At Any Visit While on Sparsentan

	Any UP/C ≤0.3 g/g (n=44)	No UP/C ≤0.3 g/g (n=64)
Baseline Prior to First Study Drug		
eGFR, mean (SD)	79.3 (39.1)	71.1 (40.4)
Documented nephrotic syndrome, n (%)	8 (18.2)	15 (23.4)
Baseline Prior to First Dose of Sparsentan		
UP/C, geometric mean	**1.7****	**3.6**
Immunosuppressive treatment, n (%)	**20 (45.5)***	**16 (25.0)**
Steroids	9 (20.5)	9 (14.1)
CNI	10 (22.7)	9 (14.1)
MMF	8 (18.2)	5 (7.8)

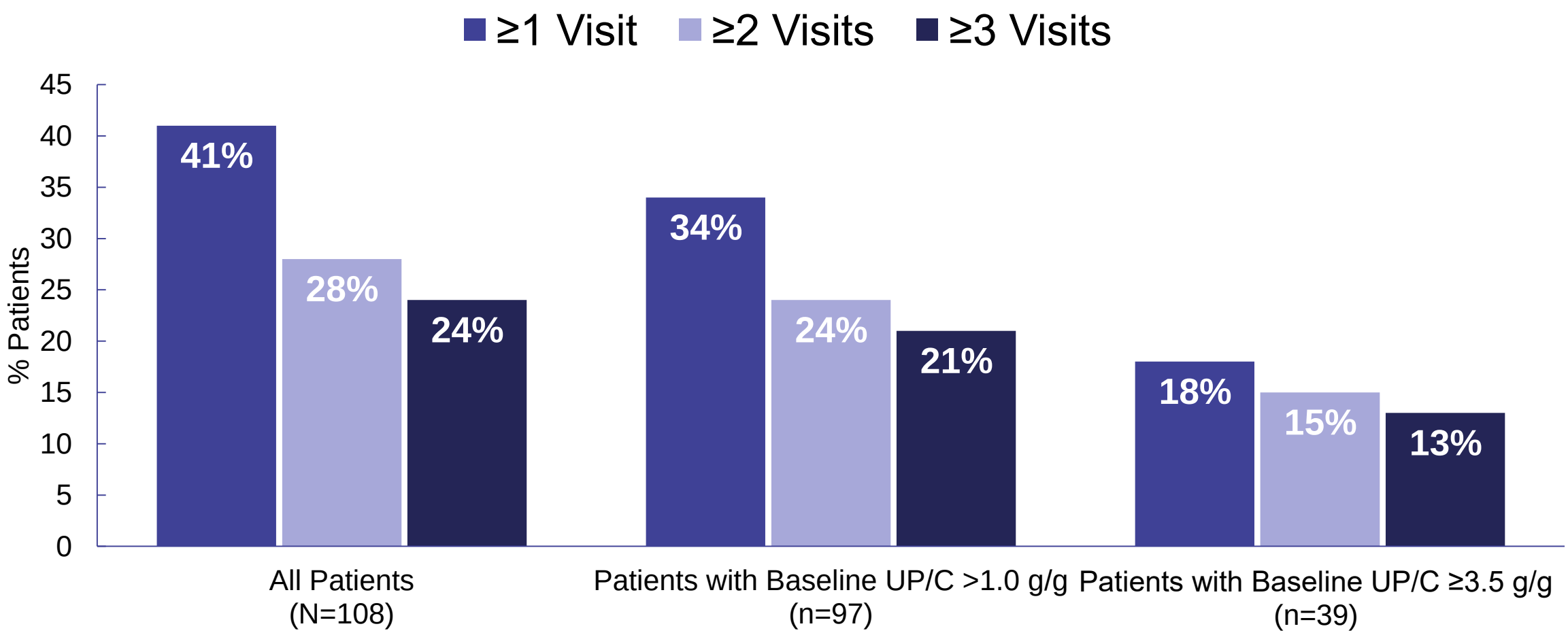
**P<0.01 compared to patients with no UP/C ≤0.3 g/g using log UP/C; n=43 in Any UP/C ≤0.3 g/g group. *P<0.05 compared to patients with no UP/C ≤0.3 g/g. CNI, calcineurin inhibitor; IST, immunosuppressive treatment; MMF, mycophenolate mofetil.

A High Percentage of Patients Achieved UP/C ≤0.3 g/g at Any Visit in a Dose-related Manner



109 patients were randomized in DUET; 108 patients received at least one dose of sparsentan and were eligible for evaluation of UP/C while on sparsentan.

Approximately 25% of All Sparsentan-treated Patients Achieved UP/C ≤0.3 g/g at Three or More Visits



Baseline UP/C is prior to first dose of sparsentan.

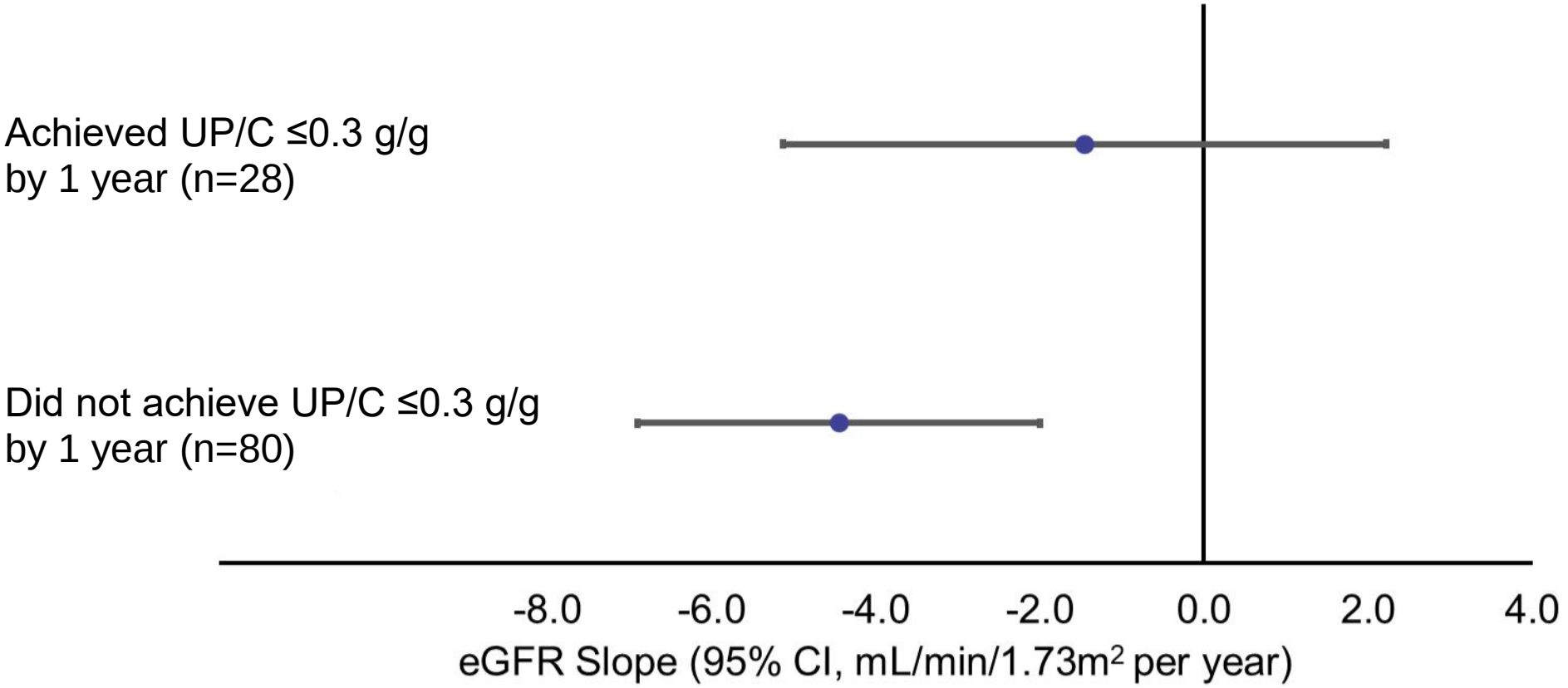
- **Median duration of UP/C follow-up while on sparsentan was 42.5 months**

Key Additional Findings

- 28/44 (64%) patients achieved UP/C ≤0.3 g/g within 1 year of the first sparsentan dose
- 24/44 (55%) patients had sustained UP/C ≤0.3 g/g
  - Median (Q1, Q3) duration of sustained complete remission was 34.4 (11.2, 43.6) months
- Consistent with previously published data, **no new safety signals** were identified up to the time of this analysis

Sustainability of complete remission of proteinuria was determined for patients with at least 2 consecutive UP/C ≤0.3 g/g and derived as the total duration beginning from UP/C ≤0.3 g/g and ending when UP/C >0.6 g/g.

Achieving Complete Remission With Sparsentan in the First Year was Associated With Slower eGFR Decline Over Two Years



Conclusions

- A high proportion of patients in the DUET trial achieved complete remission of proteinuria on at least one occasion while on sparsentan and these data support the strong relationship between reduction of proteinuria and slowing of eGFR decline

- These post-hoc analyses support the long-term nephroprotective potential of sparsentan in FSGS

- The ongoing phase 3 DUPLEX study (NCT03493685) will evaluate the long-term antiproteinuric efficacy, nephroprotective potential, and safety profile of sparsentan compared to irbesartan, in both adult and pediatric patients with FSGS over 108 weeks of randomized and double-blind treatment

Thank You to the DUET Site Physicians, Coordinators, and Patients