FP129

Newly Administered Immunosuppressive Therapy (IST) Has No Impact on Long-term Antiproteinuric Effect of Sparsentan (SPAR), a Dual Angiotensin and Endothelin Receptor Antagonist, in Patients With Primary Focal Segmental Glomerulosclerosis (FSGS): Interim Analysis of the Phase 2 DUET Trial

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Introduction

- Sparsentan is a first-in-class, orally active, dual-acting, selective antagonist of the angiotensin II Type 1 receptor and the endothelin type A receptor in development for the treatment of primary focal segmental glomerulosclerosis (FSGS)[1]
- In the 8-week, double-blind (DB) period in the phase 2 DUET trial in patients with primary FSGS, sparsentan 200, 400, and 800 mg/d resulted in greater reduction in proteinuria compared with irbesartan 300 mg/d[2]
- All patients completing the DB period entered an open-label extension (OLE) and received sparsentan, regardless of treatment in the DB period
- In an interim analysis (data cutoff: June 9, 2016), sparsentan resulted in further decline in proteinuria over 48 weeks in all groups[3]
- Potential effects of initiation of new immunosuppressive therapy (IST) on proteinuria reduction with sparsentan are of interest

Objective

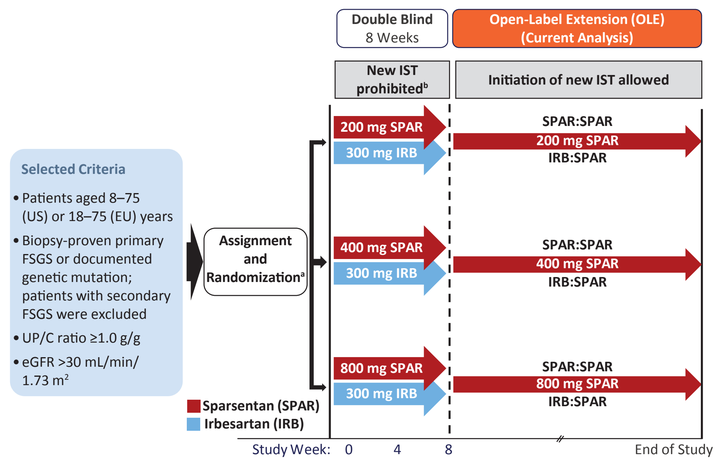
- To determine the potential impact of newly initiated IST on the effects of sparsentan treatment during the OLE in the DUET study

Methods

Study Design

- DUET (NCT01613118) is a phase 2, randomized, active-controlled study with an 8-week DB treatment period
- Patients were allocated to 200, 400, and 800 mg/d sparsentan cohorts and randomized within these cohorts to receive DB treatment with sparsentan or active control (irbesartan 300 mg/d)
- All patients completing DB treatment continued in an OLE and received only sparsentan for an additional 144 weeks at the same dose as in the original cohort
  - During the OLE, dose adjustments were allowed for safety or efficacy
- Initiation of new IST was not permitted during the 8-week DB period but was allowed during the OLE

Figure 1. DUET study design, selected inclusion criteria, and dosing



Note: Patients were assigned to dose cohort, then randomized to receive sparsentan or irbesartan within the dose cohort. Study drug was administered orally, once daily. Patients weighing ≤50 kg received half the assigned daily dose of sparsentan or irbesartan.
[a]After 2 weeks of RASI washout.
[b]If a patient was taking ISTs (except rituximab or cyclophosphamide), the dose and/or levels must have been stable for 1 month before randomization and the investigator should not have had plans to alter the regimen during the first 8 weeks of treatment, except to stabilize levels.
DB = double-blind; eGFR = estimated glomerular filtration rate; FSGS = focal segmental glomerulosclerosis; IRB:SPAR = patients randomized to irbesartan who then transitioned to sparsentan in the OLE; IST, immunosuppressive therapy; RASI = renin-angiotensin system inhibitor; SPAR:SPAR = patients randomized to sparsentan who also received sparsentan in the OLE; UP/C = urinary protein-to-creatinine ratio.

Assessments

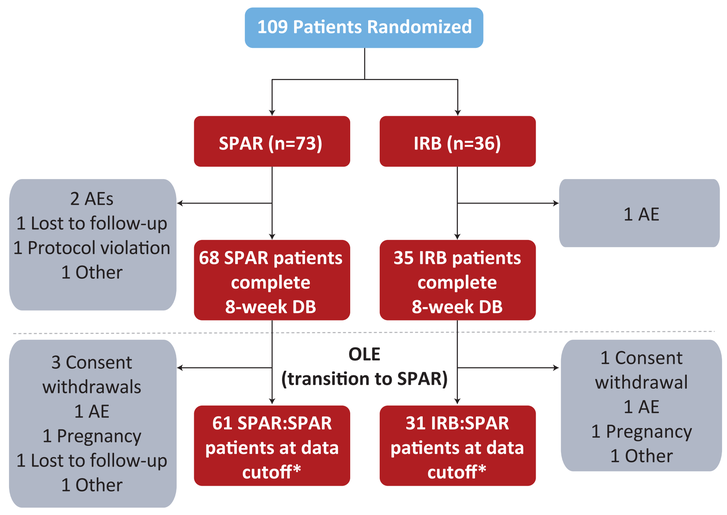
- Urinary protein-to-creatinine ratio (UP/C), estimated glomerular filtration rate (eGFR), and blood pressure (BP) over time (interim analysis through 48 weeks)
- FSGS partial remission endpoint (FPRE),[4] defined as the proportion of patients who achieved UP/C ≤1.5 g/g and a >40% reduction in UP/C, at each time point

Statistical Analysis

- This interim analysis of the OLE included follow-up through 48 weeks
- During the 8-week, DB period, the full analysis set was defined as all randomized patients who received ≥1 dose of study drug and had ≥1 post-baseline efficacy evaluation; the efficacy evaluable set included all patients who received ≥1 dose of study drug and had both baseline and Week 8 UP/C measurements
- During the OLE, the full analysis set included all patients who received open-label sparsentan and had any efficacy assessment in the OLE
- Baseline was defined as Week 0 for patients receiving SPAR:SPAR (ie, patients receiving sparsentan in the DB period and OLE), and Week 8 for patients receiving IRB:SPAR (ie, patients receiving irbesartan in the DB period and transitioning to sparsentan in the OLE)
- Changes from baseline in UP/C, eGFR, and BP were assessed through descriptive statistics
  - Statistical significance for mean change from baseline was obtained via evaluation of 95% confidence intervals (CIs); $P<0.05$ if the 95% CI excluded zero
- The analysis was repeated after truncating data from patients who received IST during the OLE
  - Only those measurements that followed the initiation of IST were excluded

Results

Figure 2. Patient disposition at interim data cutoff



*As of June 9, 2016.
AE = adverse event; DB = double-blind; 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.

Table 1. Patient demographics and baseline characteristics

Characteristics	Sparsentan, All Doses (n=73)	Irbesartan (n=36)
Age group, n (%)		
Pediatric (aged 8–18 y)	13 (18)	10 (28)
Adult (aged 19–75 y)	60 (82)	26 (72)
Sex, n (%)		
Female	32 (44)	17 (47)
Male	41 (56)	19 (53)
Race, n (%)		
Asian	5 (7)	1 (3)
Black	8 (11)	7 (19)
White	57 (78)	26 (72)
Other	3 (4)	2 (6)
Ethnicity, n (%)		
Hispanic/Latino	14 (19)	6 (17)
Non-Hispanic/Non-Latino	59 (81)	30 (83)
BMI, kg/m², mean (SD)	28.4 (6.1)	28.7 (6.4)
IST at baseline, n (%)	21 (29)	13 (36)
eGFR, mL/min/1.73 m², mean (SD)	74.6 (37.6)	73.1 (41.3)
UP/C ratio, g/g, median (range)	3.61 (0.4–18.7)	3.12 (0.9–10.7)
ACE inhibitor or ARB use before washout, n (%)	59 (81)	32 (89)
Use of ≥1 diuretic/antihypertensive agent, n (%)	40 (55)	20 (56)
Diuretics	26 (36)	9 (25)
Additional antihypertensive treatments	29 (40)	16 (44)

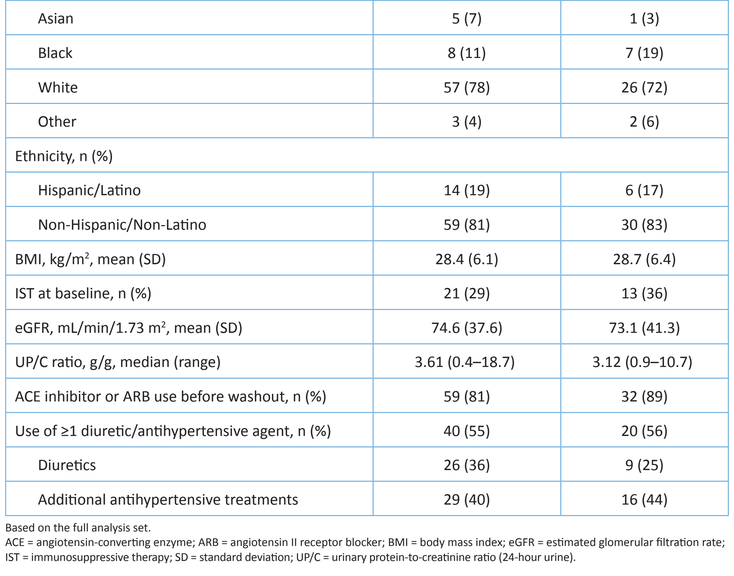
Based on the full analysis set.
ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; BMI = body mass index; eGFR = estimated glomerular filtration rate; IST = immunosuppressive therapy; SD = standard deviation; UP/C = urinary protein-to-creatinine ratio (24-hour urine).

Table 2. Patients with new IST at or before a given timepoint

Study Period	Study Week	Patients With New IST,[a] n (%)	
		SPAR:SPAR (n=50)[b]	IRB:SPAR (n=33)[b]
DB[c]	0–8	—	—
OLE	16	3 (6)	1 (3)
	24	4 (8)	1 (3)
	36	4 (8)	2 (6)
	48	6 (12)	2 (6)

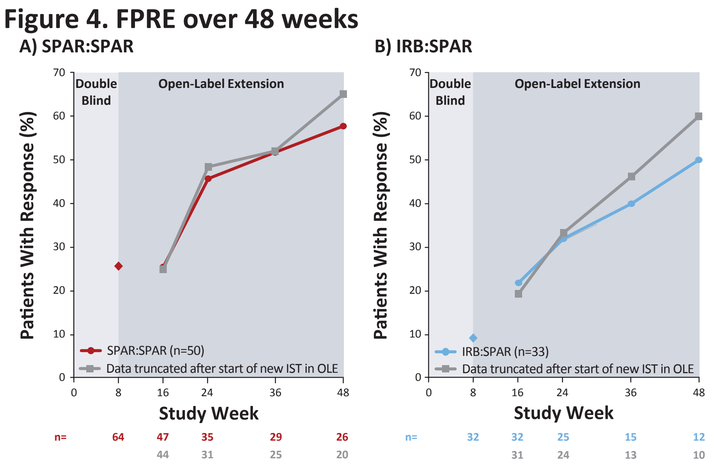
[a]IST medications that were newly initiated during the OLE were hydrocortisone, methylprednisolone, mycophenolate mofetil, prednisone, and tacrolimus.
[b]Includes all patients who received open-label sparsentan and had any efficacy assessments after receiving open-label sparsentan.
[c]Initiation of new IST was not permitted during the 8-week DB period.
DB = double blind; IRB:SPAR = patients randomized to irbesartan who then transitioned to sparsentan in the OLE; IST = immunosuppressive therapy; OLE = open-label extension; SPAR:SPAR = patients randomized to sparsentan who also received sparsentan in the OLE.

Figure 3. UP/C over 48 weeks



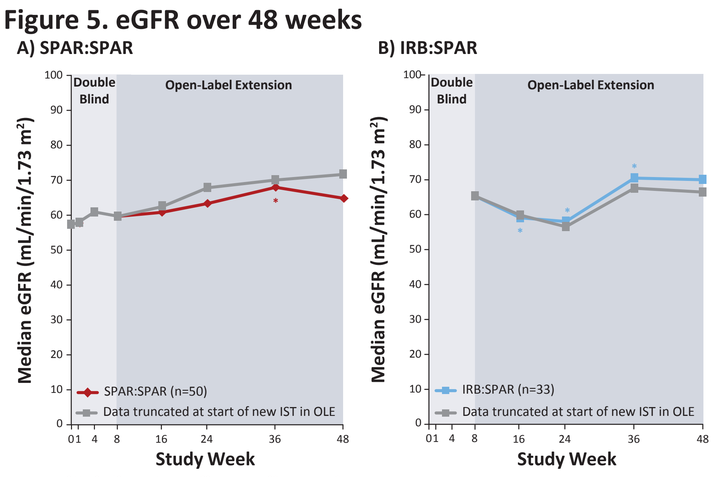
*$P<0.05$ vs baseline (Week 0 for SPAR:SPAR; Week 8 for IRB:SPAR).
IRB:SPAR = patients randomized to irbesartan who then transitioned to sparsentan in the OLE; IST = immunosuppressive therapy; OLE = open-label extension; SPAR:SPAR = patients randomized to sparsentan who also received sparsentan in the OLE; UP/C = urinary protein-to-creatinine ratio (first morning void).

Figure 4. FPRE over 48 weeks



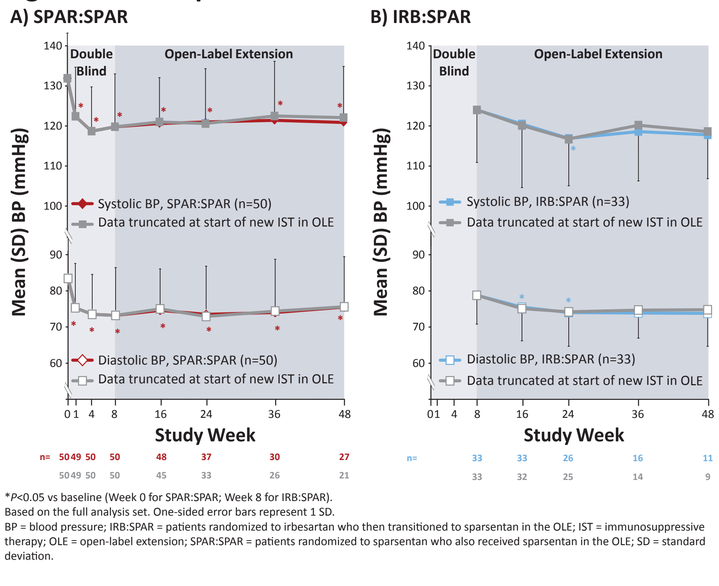
FPRE is defined as UP/C ≤1.5 g/g and >40% reduction in UP/C from baseline. Baseline in the double-blind period defined as Week 0; baseline for the open-label period defined as last observation before start of open-label sparsentan treatment (ie, Week 8). Data for Week 8 is based on the efficacy evaluable set. Data for Weeks 16–48 are based on the full analysis set.
FPRE = FSGS partial remission endpoint; IRB:SPAR = patients randomized to irbesartan who then transitioned to sparsentan in the OLE; IST = immunosuppressive therapy; OLE = open-label extension; SPAR:SPAR = patients randomized to sparsentan who also received sparsentan in the OLE; UP/C = urinary protein-to-creatinine ratio.

Figure 5. eGFR over 48 weeks



*$P<0.05$ vs baseline (Week 0 for SPAR:SPAR and Week 8 for IRB:SPAR).
Based on the full analysis set.
eGFR = estimated glomerular filtration rate; IRB:SPAR = patients randomized to irbesartan who then transitioned to sparsentan in the OLE; IST = immunosuppressive therapy; OLE = open-label extension; SPAR:SPAR = patients randomized to sparsentan who also received sparsentan in the OLE.

Figure 6. Blood pressure over 48 weeks



*$P<0.05$ vs baseline (Week 0 for SPAR:SPAR; Week 8 for IRB:SPAR).
Based on the full analysis set. One-sided error bars represent 1 SD.
BP = blood pressure; IRB:SPAR = patients randomized to irbesartan who then transitioned to sparsentan in the OLE; IST = immunosuppressive therapy; OLE = open-label extension; SPAR:SPAR = patients randomized to sparsentan who also received sparsentan in the OLE; SD = standard deviation.

Summary

Original Results

- Patients treated with sparsentan achieved progressive reduction in UP/C over 48 weeks in the OLE of the DUET study
- Transition from irbesartan to sparsentan in the OLE led to further reduction in UP/C
- eGFR remained stable during this follow-up period
- In the SPAR:SPAR group, BP declined initially and remained stable for the remainder of the follow-up period; in the IRB:SPAR group, transition to sparsentan resulted in further reduction in BP

Assessing the Impact of New IST

- Few patients initiated new IST during the OLE
- Truncation of data after initiation of new IST yielded results that were similar to those from the original analysis
- Initiating new IST had no meaningful impact on the course of proteinuria, eGFR, and BP observed under long-term treatment with sparsentan

Conclusions

- Newly initiated IST had no meaningful impact on the effects of sparsentan observed in this interim analysis over 48 weeks of sparsentan treatment (data cutoff: June 9, 2016) in the DUET OLE

References

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

Disclosures

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