FILSPARI® (sparsentan)
Dosing and Administration in Clinical Trials of FSGS

Summary

Background

- Sparsentan is an investigational therapeutic candidate for the treatment of FSGS[1,2]
- Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors[2-4]

Study Data

The DUET Study

- Patients were randomized 3:1 to receive sparsentan 200 mg/day, 400 mg/day (two cohorts), or 800 mg/day (two cohorts), or irbesartan 300 mg/day[2]

The DUPLEX Study

- Patients discontinued prescribed ARB and ACEi therapies and were then randomized 1:1 to receive 800 mg/day sparsentan or 300 mg/day irbesartan[1]

The EPPIK Study

- Sparsentan 80 mg/mL oral suspension is administered in a novel liquid formulation based on patient age and weight. For patients with FSGS or MCD, dose exposure is similar to an adult equivalent dose of 800 mg/day. For patients with IgAN, IgAV, or Alport syndrome, dose exposure is similar to an adult equivalent of 400 mg/day[5]

Background

Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors.[2-4] Preclinical studies in rodent models of chronic kidney disease have shown that blockade of both ET_A and AT_1 pathways reduces proteinuria, protects podocytes, and prevents glomerulosclerosis and mesangial cell proliferation.[6-8]

The DUET Study

The DUET study (NCT01613118) is a phase 2, randomized, multicenter, double-blind, active-control trial in patients with biopsy-proven FSGS. Patients were randomized to 1 of 3 doses (200, 400, or 800 mg/day) of sparsentan or irbesartan (300 mg/day) and maintained through an 8-week double-blind phase. The primary endpoint was defined as reduction in UPCR after 8 weeks of treatment. The proportion of patients who achieved partial FSGS remission was evaluated as a secondary endpoint. Following the double-blind phase, patients had the option to continue into a 144-week OLE of treatment with sparsentan.[2]

The DUPLEX Study

The DUPLEX study (NCT03493685) is a global, randomized, multicenter, double-blind, active-controlled, phase 3 trial examining the safety and efficacy of sparsentan as compared to irbesartan in patients aged 8 to 75 years with biopsy-proven FSGS. Patients with UPCR ≥1.5 g/g at screening, eGFR ≥30 mL/min/1.73 m^2, and mean seated BP ≥100/60 mm Hg (patients ≥18 years) or above the 5th percentile for sex and height (<18 years) were eligible. After a 2-week washout period, 371 patients were randomized to receive either sparsentan or irbesartan, and subsequently dose titrated over 2 weeks to the maximum dose of either 800 mg/day sparsentan or 300 mg/day irbesartan, as tolerated.[1,9] Patients remained on maintenance doses of sparsentan or irbesartan during a 108-week double blind phase. Standard-of-care treatment, including RAASi, was resumed in Weeks 108-112. The primary efficacy endpoint was eGFR slope over 108 weeks of treatment, defined as eGFR total slope from Day 1 to Week 108 of treatment and eGFR chronic slope from Week 6 to Week 108 (following the initial acute effect of randomized treatment). The key secondary endpoint was percent change in eGFR from baseline to 4 weeks post-cessation of randomized treatment at Week 112.[9] An additional interim endpoint was the proportion of patients achieving partial remission of proteinuria, defined as UPCR ≤1.5 g/g and a >40% reduction (FPRE) at Week 36. Proportion of patients achieving complete remission of proteinuria (UPCR <0.3 g/g) at any time in the double-blind period was also examined. Safety was assessed by double-blind monitoring of adverse events and safety endpoints.[1,9]

The EPPIK Study

The EPPIK study (NCT05003986) is a phase 2, global, open-label, single-arm, multicenter cohort study to evaluate the safety, efficacy, and PK of a liquid formulation of sparsentan in pediatric patients with selected proteinuric glomerular diseases. The primary objective of the EPPIK study is to examine long-term antiproteinuric and nephroprotective potential and safety in this pediatric population.[10] Approximately 57 pediatric patients aged ≥1 to <18 years will be enrolled. EPPIK Population 1 will include ~30 patients aged 1 to <18 years with FSGS or treatment-resistant MCD. Population 2 will include ~27 patients aged 2 to <18 years with IgAN, IgAV, or Alport syndrome. Primary endpoints are the change from baseline in UPCR over a 108-week treatment period, incidence of TEAEs, SAEs, AEs leading to treatment discontinuation, and AEs of interest. Secondary endpoints include observed plasma PK concentration, steady-state PK parameters, change from baseline in UACR and eGFR over 108 weeks of treatment, and proportion of patients with FSGS or MCD histological patterns achieving partial remission (FPRE) in UPCR. Partial remission is defined as UPCR ≤1.5 g/g and >40% reduction in UPCR. Safety parameters are monitored throughout the duration of the study.[5,10]

Study Data

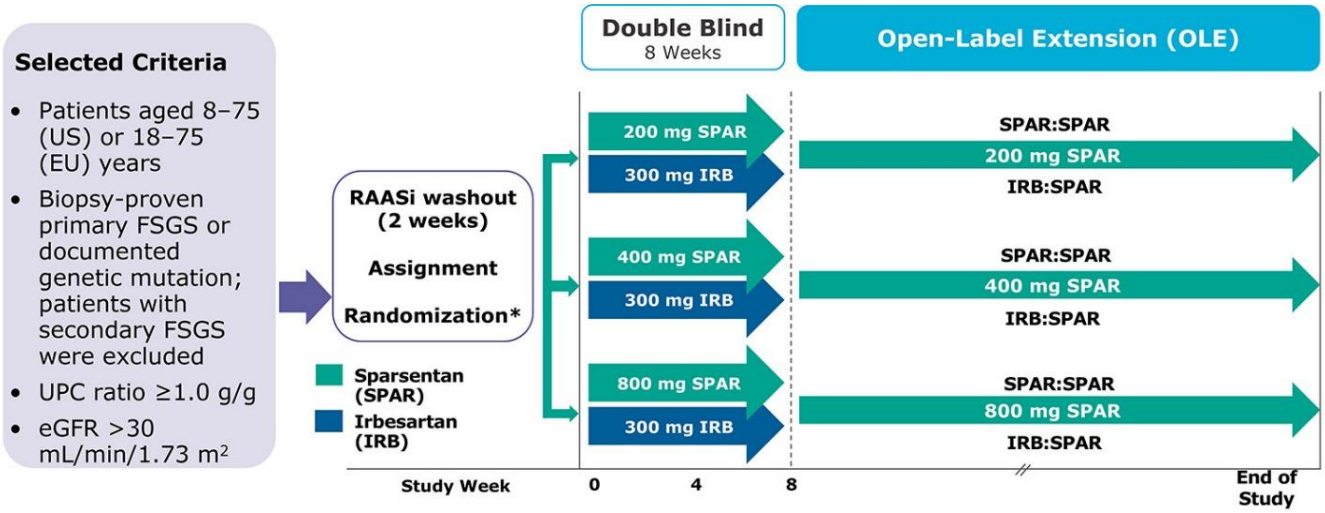
Dosing and Administration in FSGS

The DUET Study

Prior to randomization, patients discontinued prescribed ARB and ACEi therapies. Patients were then randomized 3:1 through an interactive web response system within sequential dose-escalating, 20-patient cohorts to receive sparsentan 200 mg/day, 400 mg/day (2 cohorts), or 800 mg/day (2 cohorts), or irbesartan 300 mg/day (**Figure 1**). Incremental safety reviews were performed by an independent DMC. Only patients aged 18 years and older were initially enrolled in

cohort 1 at the 200 mg/day dose. After 8 patients completed 4 weeks of treatment, a safety review was conducted and enrollment was opened to patients aged 8-17 years. Cohort 2 was also opened for randomization of patients to receive sparsentan 400 mg or irbesartan 300 mg. This process was repeated after 8 patients completed 4 weeks of treatment at 400 mg, and again after 8 patients completed 4 weeks at 800 mg. DMC reviews continued every 6 months. Patients randomized to irbesartan received 150 mg/day for the first week before escalating to 300 mg/day for the remaining 7 weeks. Patients with body weight ≤50 kg received 50% of the assigned study drug doses.[2]

Figure 1. Dosing in the DUET Study



*Patients were assigned to dose cohort, then randomized to sparsentan or irbesartan within the dose cohort. The study drug was 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. Randomization after 2 weeks RAASi washout. IRB:SPAR = patients randomized to irbesartan who then transitioned to sparsentan in the OLE; SPAR:SPAR = patients randomized to sparsentan who also received sparsentan in the OLE.

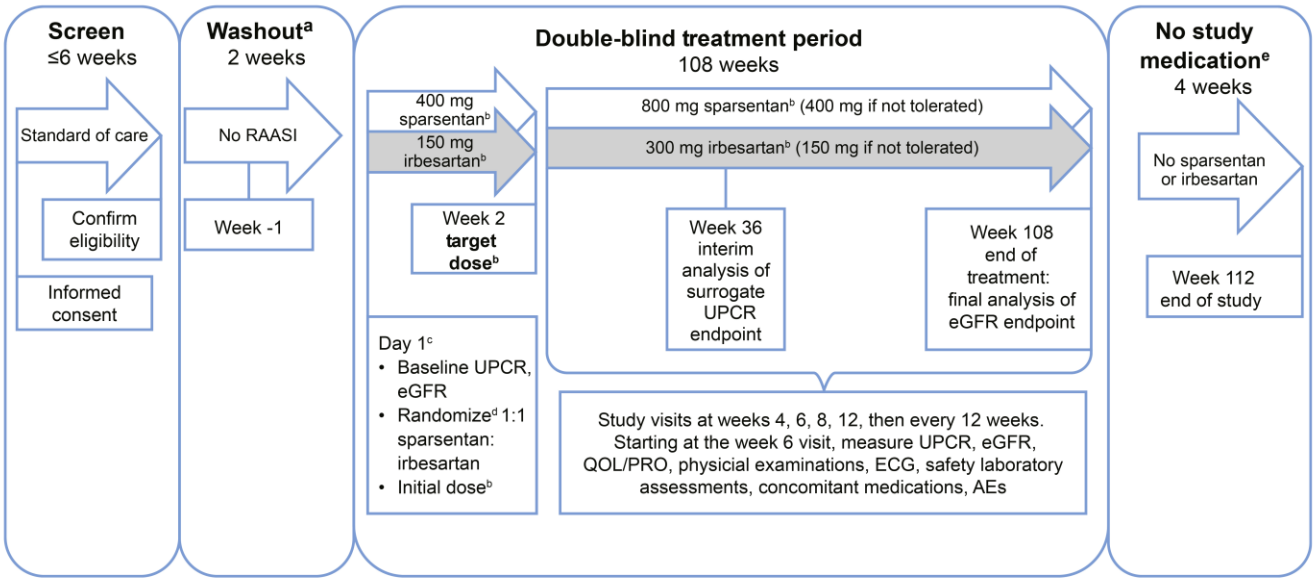
In a post-hoc assessment through 240 weeks of the DUET OLE, no new or unexpected safety signals emerged.[11]

The DUPLEX Study

Prior to randomization, patients discontinued prescribed ARB and ACEi therapies (**Figure 2**). Patients were then randomized 1:1 through an interactive web response system to 800 mg/day sparsentan or 300 mg/day irbesartan. Patients who weighed ≤50 kg at screening received half the otherwise specified doses of sparsentan or irbesartan. Randomization was stratified by eGFR (≥30 to <60 mL/min per 1.73 m^2 and ≥60 mL/min per 1.73 m^2 for all patients) and UPCR (≤3.5 g/g and >3.5 g/g [patients ≥18 years old] or ≤2 g/g and >2 g/g [patients <18 years old]) at screening. After 108 weeks, study treatment was discontinued and the investigator resumed standard-of-care treatment, including treatment with RAASi (with the exception of irbesartan) provided there were no contraindications for their use.[1]

Over 108 weeks of treatment, TEAEs were reported with similar frequency in the sparsentan (n=172, 93.5%) and irbesartan (n=174, 93%) treatment groups. Serious TEAEs occurred in 68 (37%) sparsentan-treated patients and 82 (43.9%) irbesartan-treated patients.[9]

Figure 2. Dosing in the DUPLEX Study



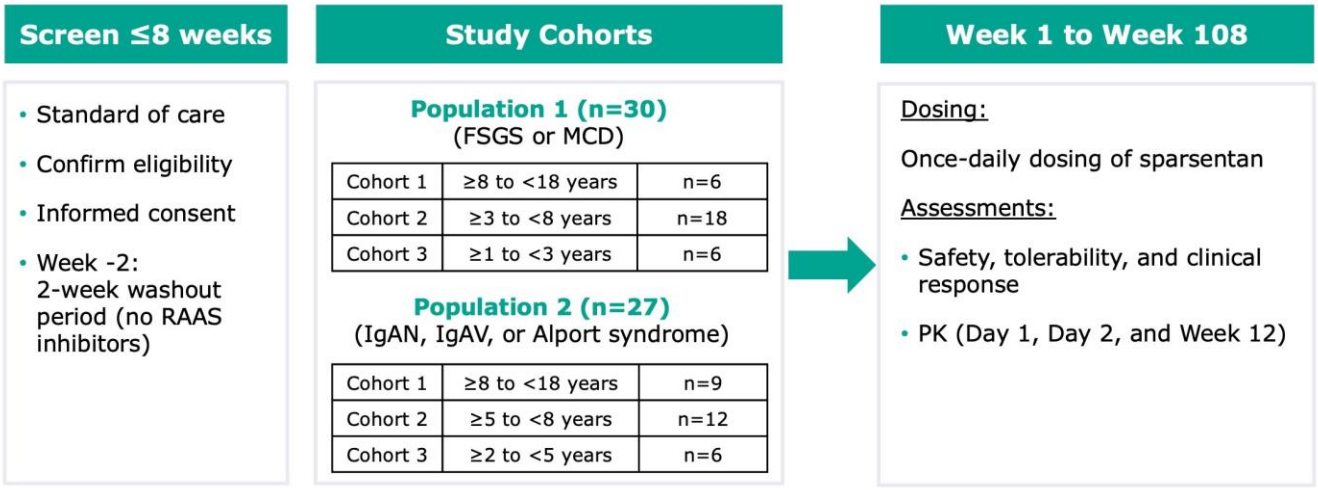
[a]For patients who are undergoing washout from RAASi. [b]Patients whose body weight is ≤50 kg at screening will receive half the otherwise specified doses of sparsentan or irbesartan (active control). Weight will be measured at each visit and the dose increased at the investigator's discretion if the patient's weight reaches >50 kg. [c]Day 1 events shown will occur in the order in which they are listed. [d]Randomization will be stratified by eGFR value (≥30 to <60 mL/min per 1.73 m^2 and ≥60 mL/min per 1.73 m^2 for all patients) and UPCR (≤3.5 g/g and >3.5 g/g [patients ≥18 years old] or ≤2 g/g and >2 g/g [patients <18 years old]) at screening. [e]Following the 108-week blinded treatment period, treatment with study medication will be discontinued. At this time, the investigator should resume standard-of-care treatment, including treatment with RAASi (with the exception of irbesartan) provided there are no contraindications for their use. The investigator may make additional adjustments in antihypertensive medications as clinically indicated to adequately control the patient's BP.

Dosing and Administration in the EPPIK Study

Study Design

Prior to enrollment, patients taking RAASi will undergo a 2-week washout period. Other antihypertensive medications, except endothelin inhibitors, are allowed for treatment of patients with hypertension. Following enrollment into Population 1 or 2, patients are further stratified into cohorts according to age. Patients are evaluated over 108 weeks and treated with once-daily dosing of liquid sparsentan. Patients are then returned to SOC for 4 weeks of follow-up. Safety, tolerability, and clinical response are assessed throughout the study (**Figure 3**).[5,10]

Figure 3. EPPIK Study Design



Patients are randomly assigned to a PK assessment schedule. For all patients, PK plasma levels are assessed pre-dose on Day 1 and Week 12; an additional pre-dose PK plasma level measurement occurs on Day 2, ~24 hours after the first sparsentan dose on Day 1. At clinic visits following Week 12, plasma PK is assessed at either 1 hour and 2 hours post-dose, 2 hours and 4 hours post-dose, or 4 hours and 6 hours post-dose, depending upon the patient's assigned PK sampling schedule.[10]

Study Treatment

Sparsentan 80 mg/mL oral suspension is administered in a novel liquid formulation; starting and target doses are determined based on patient age and weight (**Table 1**). For patients in Population 1 (FSGS or MCD), dose exposure is similar to an adult equivalent dose of 800 mg/day. For patients in Population 2 (IgAN, IgAV, or Alport syndrome), dose exposure is similar to an adult equivalent of 400 mg/day. Dosing titration is determined by patient age. Patients aged ≥2 years begin with 50% of the target dose and continue to Week 2; if tolerated, dose is increased to target. Patients aged <2 years begin with 25% of target dose up to Week 2; if tolerated, dose is increased to 50% target to Week 4. If tolerated at 50%, dose is increased to target. If necessary, doses may be modified, temporarily halted, or discontinued.[10]

Table 1. Dosing in the EPPIK Study

Weight (kg)	Sparsentan 80 mg/mL					
	Population 1 (FSGS or MCD) Permitted Doses as % Target Dose			Population 2 (IgAN, IgAV, or Alport Syndrome) Permitted Doses as % Target Dose		
	25%	50%	100%	25%	50%	100%
≥2 years						
≥40	2.5 mL	**5 mL**	10 mL (800 mg)	1.25 mL	**2.5 mL**	5 mL (400 mg)
30 to <40	1.875 mL	**3.75 mL**	7.5 mL (600 mg)	0.938 mL	**1.875 mL**	3.75 mL (300 mg)
20 to <30	1.25 mL	**2.5 mL**	5 mL (400 mg)	0.625 mL	**1.25 mL**	2.5 mL (200 mg)
<20	0.625 mL	**1.25 mL**	2.5 mL (200 mg)	0.313 mL	**0.625 mL**	1.25 mL (100 mg)
<2 years				Not Applicable		
10 to <20	**0.625 mL**	1.25 mL	2.5 mL (200 mg)			
7 to <10	**0.313 mL**	0.625 mL	1.25 mL (100 mg)			

Bold indicates starting doses.

At data cutoff (April 5, 2023), 23 pediatric patients enrolled in the EPPIK study have received ≥1 dose of sparsentan oral suspension.[5,10] Sparsentan appeared to be safe and well-tolerated.[5]

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin receptor blocker; AT_1, angiotensin II type 1; BP, blood pressure; DMC, data monitoring committee; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ET_A, endothelin-1 type A; FPRE, FSGS partial remission endpoint; FSGS, focal segmental glomerulosclerosis; IgAN, immunoglobulin A nephropathy; IgAV, immunoglobulin A-associated vasculitis; IRB, irbesartan; MCD, minimal change disease; OLE, open-label extension; PK, pharmacokinetics; PRO, patient-reported outcome; QOL, quality of life; RAAS, renin-angiotensin-aldosterone system; RAASi, renin-angiotensin-aldosterone system inhibitor; SAE, serious adverse event; SOC, standard of care; SPAR, sparsentan; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

References

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