FILSPARI® (sparsentan)

SPARTACUS (Phase 2 Study): Sparsentan in Combination With SGLT2 Inhibitors Study Design

Summary

Background

- Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors[1-3]
- SPARTACUS is an open-label, multicenter, single-group phase 2 trial investigating the safety and efficacy of sparsentan in patients with IgA nephropathy at risk for disease progression despite treatment with combined RAASi and SGLT2 inhibitors[4,5]
- The SPARTACUS study began enrollment in May 2023 and is currently recruiting[4]

Background

Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors.[1-3] 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]

SGLT2 Inhibitors

SGLT2, located in the proximal segment of the nephron, is responsible for ~90% of sodium-mediated glucose reabsorption in the tubular filtrate. Inhibition of SGLT2 function within the kidney reduces glucose reabsorption and increases urinary glucose excretion in an insulin-independent manner. Sodium is in turn delivered to the macula densa, which activates tubuloglomerular feedback, reduces intraglomerular pressure, and limits podocyte damage.[9]

SGLT2 inhibitors are utilized as supportive care in patients with chronic kidney disease, including IgA nephropathy.[10,11] Studies of patients with CKD has found that treatment with SGLT2 inhibitors reduces adverse kidney outcomes.[11]

The SPARTACUS Study

The SPARTACUS study (NCT05856760) is a single-group, multicenter, open-label, exploratory phase 2 trial examining the safety and efficacy of sparsentan in adult patients with biopsy-proven IgA nephropathy at risk of disease progression despite ongoing treatment with RAASi and SGLT2 inhibitors.[5] Approximately 60 patients aged 18 years and older will be enrolled. Patients must be on stable doses of an ACEi/ARB and SGLT2 inhibitors for ≥12 weeks prior to enrollment and throughout the screening period. The primary outcome measure is change from baseline in UACR at Week 24. Secondary outcome measures include UACR <0.2 g/g at Week 24, 30% and 50% reduction from baseline in UACR at Week 24, and change from baseline in UACR, UPCR, eGFR, SBP,

and DBP at each study visit. Safety assessments throughout the study include TEAEs, SAEs, AEs leading to treatment discontinuation, and AEs of interest (**Table 1**).[4,5]

Table 1. Safety and Efficacy Endpoints in the SPARTACUS Study*

Efficacy Endpoints	Safety Endpoints

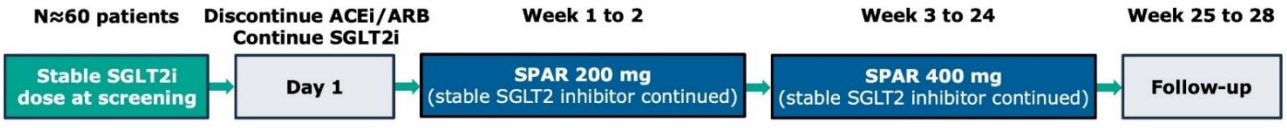
Primary
Change from baseline† in UACR‡,§
 	
Secondary
• Achievement of
  ○ UACR <0.2 g/g§
  ○ 30% reduction from baseline in UACR§
  ○ 50% reduction from baseline in UACR§
• Change from baseline† at each visit in
  ○ UACR
  ○ UPCR
  ○ eGFR
  ○ Blood pressure
	• TEAEs
	• Serious AEs
	• AEs of interest
	• AEs leading to treatment discontinuation
	• Changes from baseline† in:
	  ○ Body weight
	  ○ Vital signs
	  ○ Physical examinations
	  ○ Peripheral edema
	  ○ Clinical laboratory parameters

*Safety and efficacy will be summarized using descriptive statistics and evaluated in an interim analysis that will be performed 24 weeks after approximately 20 patients have been enrolled.
†Baseline will be defined as the last observation prior to the first dose of sparsentan.
‡Based on first morning void samples.
§At week 24.

Study Design

Patients aged 18 years and older must be on stable doses of an ACEi/ARB and SGLT2 inhibitors for ≥12 weeks prior to enrollment and throughout the screening period. Patients will discontinue ACEi/ARB medications one day before study Day 1 and maintain treatment with SGLT2 inhibitors during the course of the trial. Treatment with sparsentan will be administered daily as a 200-mg oral tablet beginning with study Day 1 with a target goal of 400 mg/day at Week 3 and continued for 24 weeks. Following the 24-week treatment period, sparsentan will be discontinued for 4 weeks, after which SOC RAASi treatment will resume. Patients will undergo a final safety visit at Week 28. Study design and eligibility criteria are presented in **Figure 1**.[4,5]

Figure 1. SPARTACUS Study Design



Key Eligibility Criteria:
- ≥18 years
- Biopsy-proven IgAN
- UACR ≥0.3 g/g
- eGFR ≥25 mL/min/1.73 m²
- Stable SGLT2i for ≥12 weeks
- Stable ACEi/ARB for ≥12 weeks

The SPARTACUS study began enrollment in May 2023 and is currently recruiting. Approximately 30 study sites are planned in the US and Hong Kong. Safety and efficacy results are expected by late 2024.[4]

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin receptor blocker; AT_1, angiotensin II type 1; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; DBP, diastolic blood pressure; ET_A, endothelin-1 type A; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; RAASi, renin-angiotensin-aldosterone system inhibitor; SAE, serious adverse event; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter-2; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SOC, standard of care; SPAR, sparsentan; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio; US, United States.

References

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