Sparsentan and Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2is) in the PROTECT Open-Label Extension (OLE) Substudy and SPARTACUS: Trials in Progress

Isabelle Ayoub,[1] Radko Komers,[2] Alex Mercer,[3] Priscila Preciado,[2] Sydney Tang,[4] Brad Rovin[1]

[1]Division of Nephrology, Ohio State University Wexner Medical Center, Columbus, OH, USA; [2]Travere Therapeutics, Inc., San Diego, CA, USA; [3]JAMCO Pharma Consulting, Stockholm, Sweden; [4]Division of Nephrology, The University of Hong Kong, Queen Mary Hospital, Pok Fu Lam, Hong Kong

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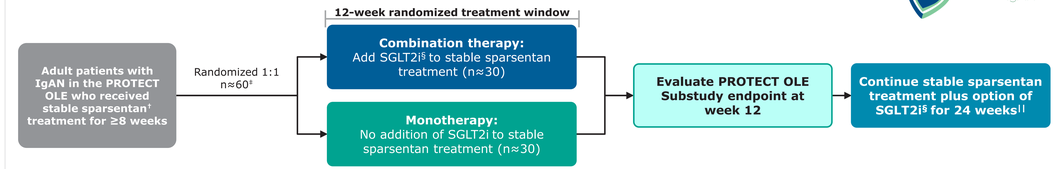
METHODS

PROTECT OLE Substudy (IgAN)

PROTECT OLE Substudy Design (NCT03762850)*



IgAN, immunoglobulin A nephropathy; OLE, open-label extension; SGLT2i, sodium-glucose cotransporter-2 inhibitor.
*Patients with IgAN who were enrolled in the phase 3 PROTECT trial initially entered a double-blind period where they were randomized 1:1 to receive sparsentan or irbesartan for up to 110 weeks, followed by 4 weeks without the study drug. Those who completed the double-blind period and met eligibility criteria could then be enrolled into the PROTECT OLE to receive sparsentan for up to 156 additional weeks. Those enrolled in the PROTECT OLE who were eligible could also participate in the randomized, open-label, controlled Substudy where they received an SGLT2i added to ongoing sparsentan therapy or ongoing sparsentan therapy without the addition of an SGLT2i. †Sparsentan was administered at a target dose of 400 mg/day. ‡The sample size for the Substudy was determined empirically without formal statistical assumptions. §The SGLT2i dapagliflozin was administered at a target dose of 10 mg/day. ‖After 12 weeks of randomized treatment, all patients may receive an SGLT2i (alongside ongoing sparsentan therapy) for up to 24 weeks or until the end of the OLE, whichever is shortest.

Key Eligibility Criteria for the PROTECT OLE Substudy

✓ Key inclusion criteria

- Urine protein excretion ≥0.3 g/day
- eGFR ≥25 mL/min/1.73 m^2
- ≥8 weeks of stable sparsentan treatment in the OLE with ≥12 weeks of the study remaining
- Permitted to receive dapagliflozin (SGLT2i) per local label

⊘ Key exclusion criteria

- End-stage kidney disease requiring kidney replacement therapy
- Received an SGLT2i ≤12 weeks prior

eGFR, estimated glomerular filtration rate; OLE, open-label extension; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

- The PROTECT double-blind period started in December 2018; recruitment has concluded
- There are PROTECT OLE Substudy sites in 16 countries

Locations With PROTECT OLE Substudy Sites

Australia, Belgium, Croatia, Czech Republic, Estonia, Hong Kong, Italy, Lithuania, New Zealand, Poland, Portugal, Republic of Korea, Spain, Taiwan, UK, USA

OLE, open-label extension.

Endpoints for the PROTECT OLE Substudy*

Safety endpoints

- Changes from baseline† in:
  - Body weight
  - Vital signs
  - Physical examination
  - Peripheral edema
  - Clinical laboratory parameters
- TEAEs, SAEs, AEOIs, and AEs leading to treatment discontinuation

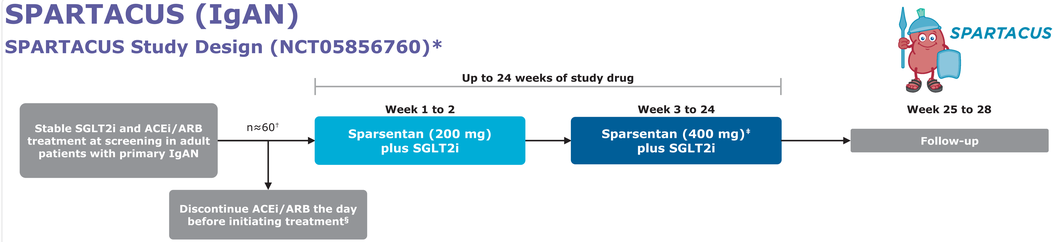
Efficacy endpoints

- Changes from baseline† in:
  - UPCR
  - UACR
  - eGFR
- Achievement of UPE <0.3 g/day

AE, adverse event; AEOI, adverse events of interest; eGFR, estimated glomerular filtration rate; OLE, open-label extension; SAE, serious adverse event; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio; UPE, urine protein excretion.
*Safety and efficacy endpoints will be summarized using descriptive statistics and presented by randomized treatment group and overall. Endpoints will be evaluated at week 12.
†Baseline will be defined as the visit in which eligibility is assessed.

SPARTACUS (IgAN)

SPARTACUS Study Design (NCT05856760)*



ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; IgAN, immunoglobulin A nephropathy; SGLT2i, sodium-glucose cotransporter-2 inhibitor. *This is a phase 2, exploratory, open-label trial for patients receiving stable SGLT2i treatment that will be continued for the duration of the study. †The sample size was determined empirically without formal statistical assumptions. ‡Sparsentan will be titrated up to a 400-mg target dose at the start of week 3 if tolerated and determined safe by the investigator. §The final dose of an ACEi and/or ARB will be taken on the day before the day 1 visit.

Key Eligibility Criteria for SPARTACUS

✓ Key inclusion criteria

- Aged ≥18 years
- Biopsy-proven IgAN
- UACR ≥0.3 g/g
- eGFR ≥25 mL/min/1.73 m^2
- ≥12 weeks of stable SGLT2i treatment
- ≥12 weeks of stable ACEi and/or ARB therapy*

⊘ Key exclusion criteria

- Secondary IgAN or IgAV
- Received sparsentan ≤12 weeks prior

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; IgAV, immunoglobulin A vasculitis; SGLT2i, sodium-glucose cotransporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio.
*ACEi and/or ARB therapy should have been administered at the maximum tolerated dose, and at least half of the maximum labeled dose.

- SPARTACUS started in May 2023; recruitment is ongoing
- Approximately 30 study sites in 2 locations are planned

Locations With SPARTACUS Study Sites

Hong Kong, USA

Endpoints for SPARTACUS*

Safety endpoints

- TEAEs
- Serious AEs
- AEs of interest
- AEs leading to treatment discontinuation
- Changes from baseline† in
  - Body weight
  - Vital signs
  - Physical examination
  - Peripheral edema
  - Clinical laboratory parameters

Efficacy 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
  - eGFR
  - UPCR
  - Blood pressure

AE, adverse event; eGFR, estimated glomerular filtration rate; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.
*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.

INTRODUCTION

- Sparsentan is a nonimmunosuppressive, single-molecule, dual endothelin angiotensin receptor antagonist (DEARA)[1–3]
- Based on results from the PROTECT trial of patients with immunoglobulin A nephropathy (IgAN),[4] sparsentan was granted accelerated approval by the US Food and Drug Administration for adults with primary IgAN at risk of rapid disease progression[5]
- SGLT2is reduced the risk of progression to kidney failure with IgAN in subgroup analyses from DAPA-CKD and EMPA-KIDNEY.[6,7] SGLT2i plus DEARA combination therapy may provide therapeutic benefit due to potentially additive kidney protection
- Here, we present the study designs of 2 ongoing complementary trials, the PROTECT OLE Substudy (NCT03762850) and SPARTACUS (NCT05856760), which are investigating sparsentan plus SGLT2i combination therapy in adult patients with IgAN

OBJECTIVE

- The PROTECT OLE Substudy and SPARTACUS will investigate the safety and efficacy of sparsentan plus SGLT2i combination therapy in adult patients with IgAN

SUMMARY

Together, these 2 complementary studies will evaluate the safety and efficacy of concomitant sparsentan plus SGLT2i treatment in adults with IgAN by evaluating the clinical benefit of adding SGLT2i treatment to stable sparsentan therapy in the PROTECT OLE Substudy or by adding sparsentan treatment to stable SGLT2i treatment in SPARTACUS

Safety and efficacy results are expected from both the PROTECT OLE Substudy and SPARTACUS by late 2024

DISCLOSURES

IA reports a contract with George Clinical for being US national leader on SPARTACUS (payment to their institution for salary support); payment from Travere Therapeutics, Inc.; payment from Sanofi and Aurinia for participation in data safety monitoring board or advisory board; and leadership or fiduciary role (unpaid) in the SCM24 program committee; **RK** is an employee of Travere Therapeutics, Inc., and may have equity or other financial interest in Travere Therapeutics, Inc.; **AM** reports consulting fees from Travere Therapeutics, Inc., through a contract with JAMCO Pharma Consulting and consulting fees from Vera Therapeutics; **PP** is an employee of Travere Therapeutics, Inc., and may have equity or other financial interest in Travere Therapeutics, Inc.; **ST** reports payment or honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, GSK, and Novartis; role as president of the Asian Pacific Society of Nephrology; and role on executive committee of KDIGO; **BR** reports consulting fees and clinical trial funding to his institution from Travere Therapeutics, Inc.

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Contact information: Isabelle Ayoub, isabelle.ayoub@osumc.edu

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