Concomitant Sparsentan and Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i) in Patients With IgA Nephropathy (IgAN) in the PROTECT Open-Label Extension (OLE)

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RESULTS

Patient Population

- At data cutoff, 39 patients had received sparsentan with concomitant SGLT2i treatment in the OLE period
  - Five patients discontinued the OLE, including 2 who first discontinued SGLT2i treatment and then discontinued the OLE
    - Discontinuations were due to kidney replacement therapy (n=1), physician decision (n=1), and TEAEs (n=3; aggravation of IgAN [n=1] and alanine aminotransferase elevation [n=2])
  - Two patients discontinued SGLT2i treatment but are continuing to receive sparsentan treatment in the OLE (reasons for discontinuing concomitant medications were not captured)
- Baseline patient demographics and clinical characteristics are reported in **Table 1** and **Table 2**, respectively

Table 1. Patient Demographics

Baseline characteristic*	Patients (N=39)
Sex, n (%)	
Male	28 (72)
Female	11 (28)
Race, n (%)	
White	25 (64)
Asian	11 (28)
Black/African American	2 (5)
Other	1 (3)
Ethnicity, n (%)	
Not Hispanic/Latino	38 (97)
Hispanic/Latino	1 (3)
Age at baseline visit, mean (SD), years	44.2 (11.11)

OLE, open-label extension; SGLT2i, sodium-glucose cotransporter-2 inhibitor.
*Baseline was defined as the OLE visit closest to the SGLT2i start (ie, before or <14 days after).

Table 2. Baseline Clinical Characteristics and Medication Use

Baseline characteristic	Patients (N=39)
Clinical measurements	
BMI, mean (SD), kg/m^2	28.4 (4.59)*
Body weight, mean (SD), kg	85.4 (23.13)*
Systolic blood pressure, mean (SD), mm Hg	126.2 (12.65)*
Diastolic blood pressure, mean (SD), mm Hg	81.4 (9.95)*
Urine protein excretion, g/day	
Mean (SD)	2.7 (1.83)
Median (IQR)	2.0 (1.3-4.2)
UPCR, g/g	
Mean (SD)	1.97 (1.20)
Median (IQR)	1.77 (1.06-3.15)
eGFR, mL/min/1.73 m^2	
Mean (SD)	44.9 (22.39)†
Median (IQR)	38.0 (29.0-53.0)
History of hypertension, n (%)	30 (77)
Antihypertensive medications at baseline visit, n (%)	24 (62)
Diuretics	13 (33)
β-Blockers	11 (28)
α-Blockers	6 (15)
Calcium channel blockers	14 (36)
Time from start of OLE treatment to start of SGLT2i treatment, median (IQR), days	253.0 (92.0-358.0)

BMI, body mass index; eGFR, estimated glomerular filtration rate; IQR, interquartile range; OLE, open-label extension; SGLT2i, sodium-glucose cotransporter-2 inhibitor; UPCR, urine protein-to-creatinine ratio.
*n=37. †n=38.

Safety

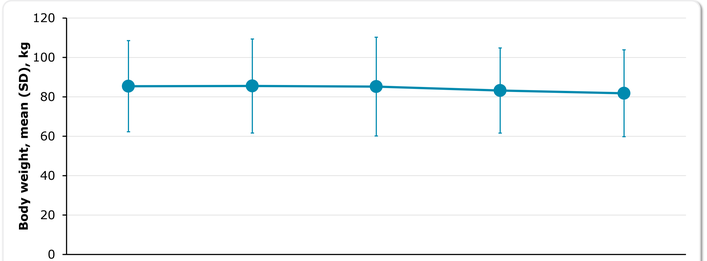
- Twenty-six patients (67%) had a TEAE (**Table 3**)
- Body weight (**Figure 1**) and blood pressure (systolic and diastolic; **Figure 2**) remained relatively stable over time following the addition of an SLGT2i to sparsentan treatment

Table 3. Summary of TEAEs

TEAEs*	Patients (N=39)
Patients with any TEAE, n (%)	26 (67)
TEAEs in >1 patient, n (%)	
Hyperkalemia	5 (13)
COVID-19	4 (10)
Hypertension	3 (8)
Acute kidney injury	2 (5)
Chronic kidney disease	2 (5)
Headache	2 (5)
Hypotension	2 (5)
Peripheral edema	2 (5)
Viral infection	2 (5)

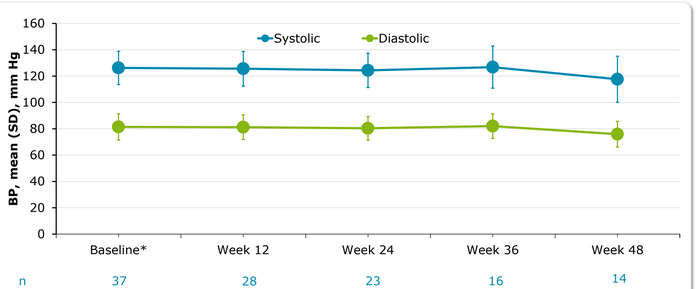
MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event. *TEAEs were based on MedDRA preferred terms.

Figure 1. Body Weight Over Time



OLE, open-label extension; SGLT2i, sodium-glucose cotransporter-2 inhibitor.
*Baseline was defined as the OLE visit closest to the SGLT2i start (ie, before or <14 days after start of SGLT2i treatment). Data are shown at weeks 12, 24, 36, and 48 after baseline.

Figure 2. Systolic and Diastolic Blood Pressure Over Time

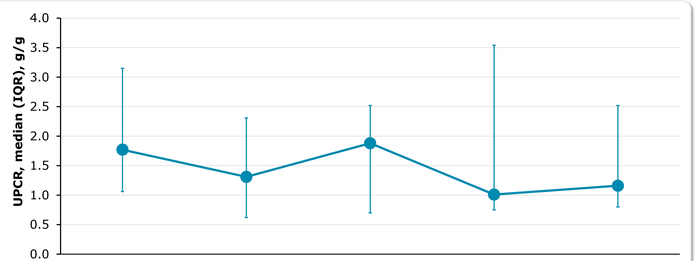


BP, blood pressure; OLE, open-label extension; SGLT2i, sodium-glucose cotransporter-2 inhibitor.
*Baseline was defined as the OLE visit closest to the SGLT2i start (ie, before or <14 days after start of SGLT2i treatment). Data are shown at weeks 12, 24, 36, and 48 after baseline.

Efficacy

- Combination therapy of sparsentan plus an SGLT2i led to a further reduction in proteinuria for up to 48 weeks (**Figure 3**)

Figure 3. UPCR Over Time



IQR, interquartile range; OLE, open-label extension; SGLT2i, sodium-glucose cotransporter-2 inhibitor; UPCR, urine protein-to-creatinine ratio.
*Baseline was defined as the OLE visit closest to the SGLT2i start (ie, before or <14 days after start of SGLT2i treatment). Data are shown at weeks 12, 24, 36, and 48 after baseline.

CONCLUSIONS

- Early clinical experience of patients during the PROTECT OLE period shows that an SGLT2i added to stable sparsentan treatment is generally well tolerated
- Data are consistent with an additive benefit on proteinuria reduction with combination therapy
- A randomized substudy within the PROTECT OLE period is further investigating the safety and efficacy of sparsentan with or without concomitant SGLT2i treatment

DISCLOSURES

LK is the PI for sponsor studies from Akebia Therapeutics, AstraZeneca, Boehringer Ingelheim, CARA Therapeutics, Chinook Therapeutics, CSL Behring, Galderma, Omeros, Otsuka, Reata Pharmaceuticals, Sanifit, Travere Therapeutics, Inc., and Visterra. **RM** has received speaker's honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Berlin-Chemie Menarini, and Lilly. **PP** is an employee and stockholder of Travere Therapeutics, Inc. **PH** is a former employee of Travere Therapeutics, Inc. **AM** has received consultancy fees from Travere Therapeutics, Inc.

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INTRODUCTION

- Sparsentan is a nonimmunosuppressive, single-molecule, dual endothelin angiotensin receptor antagonist (DEARA)[1-3]
- In the ongoing PROTECT trial, sparsentan was directly compared with irbesartan in patients with IgAN.[4] Based on results from this trial, sparsentan was granted accelerated approval in the US for adults with primary IgAN at risk of rapid disease progression[5]
- Subgroup analyses from DAPA-CKD and EMPA-KIDNEY suggest that SGLT2is may reduce the progression of IgAN.[6,7] An SGLT2i plus DEARA combination therapy may provide additional kidney-protective effects, although the adverse events (AEs) with this combination therapy are unknown
- Here we report the early clinical experience of patients with IgAN enrolled in the PROTECT OLE who received an SGLT2i in addition to their ongoing sparsentan treatment

Objective

- The PROTECT OLE study will investigate the long-term efficacy, safety, and tolerability of sparsentan treatment in adult patients with IgAN
  - This analysis will assess the safety and efficacy in a subset of patients within the PROTECT OLE period who chose to add SGLT2i treatment to their ongoing sparsentan treatment

METHODS

Study Design

- Patients who completed the PROTECT double-blind period and met eligibility criteria were enrolled in the PROTECT OLE (NCT03762850)
- All patients in the PROTECT OLE will receive sparsentan with a target dose of 400 mg/day for up to 156 weeks
- Patients could initiate concomitant SGLT2i treatment at any time during the OLE period at the discretion of the investigator
  - Patients enrolled in the PROTECT OLE SGLT2i substudy, randomized (1:1) to receive sparsentan monotherapy vs sparsentan plus an SGLT2i, were excluded from this analysis
- Body weight, systolic and diastolic blood pressure, and urine protein-to-creatinine ratio (based on a 24-hour urine sample) were evaluated at baseline and at weeks 12, 24, 36, and 48 after baseline
  - Baseline was defined as the OLE visit closest to the SGLT2i start (ie, before or <14 days after)
- Treatment-emergent adverse events (TEAEs) were determined

Eligibility Criteria

- Key inclusion criteria
  - Enrollment and active participation in the PROTECT OLE period while continuing sparsentan treatment
  - Initiation of an SGLT2i as concomitant medication during the OLE period
- Key exclusion criterion
  - Enrollment in the randomized PROTECT OLE SGLT2i substudy

Statistical Analysis

- Safety and efficacy endpoints were summarized using descriptive statistics for patients who received ≥1 dose of sparsentan plus an SGLT2i

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