Poster WCN24-AB-752

# Concomitant Sparsentan and Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2is) in Patients With IgA Nephropathy (IgAN) in the PROTECT Open-Label Extension (OLE)

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TRAVERE THERAPEUTICS

# DISCLOSURES

- **PP** and **NAMA** are employees of Travere Therapeutics, Inc., and may have equity or other financial interests in Travere Therapeutics, Inc.
- **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, Berlin-Chemie Menarini, Boehringer Ingelheim, Fresenius Kabi, Novartis, Novo Nordisk and Lilly and travel support from Aurovitas Pharma and Menarini
- **AM** has received consultancy fees from Travere Therapeutics, Inc.

These data were previously presented at the American Society of Nephrology (ASN) Kidney Week 2023; November 2-5 2023; Philadelphia, PA, USA.

- 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

METHODS

## 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

# 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).

RESULTS

# 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)$^{\dagger}$ |
| 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; OLE, open-label extension; SGLT2i, sodium-glucose cotransporter-2 inhibitor; UPCR, urine protein-to-creatinine ratio.
*n=37. $^{\dagger}$n=38.

## Safety

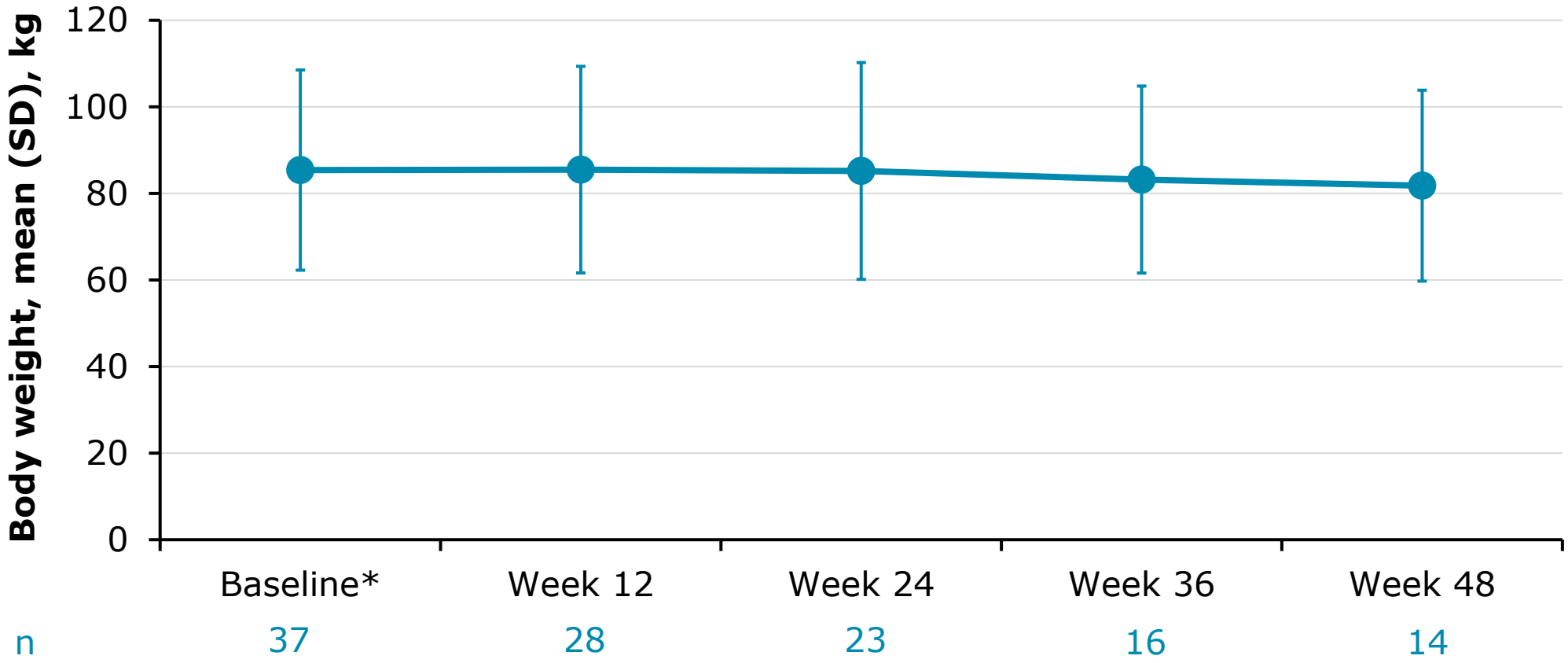
- Twenty-six patients (67%) had a TEAE (**Table 3**)
- Body weight (**Figure 1**) and blood pressure (systolic and diastolic; **Figure 2**) remained relatively stable over time following the addition of an SGLT2i to sparsentan treatment

## 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) |

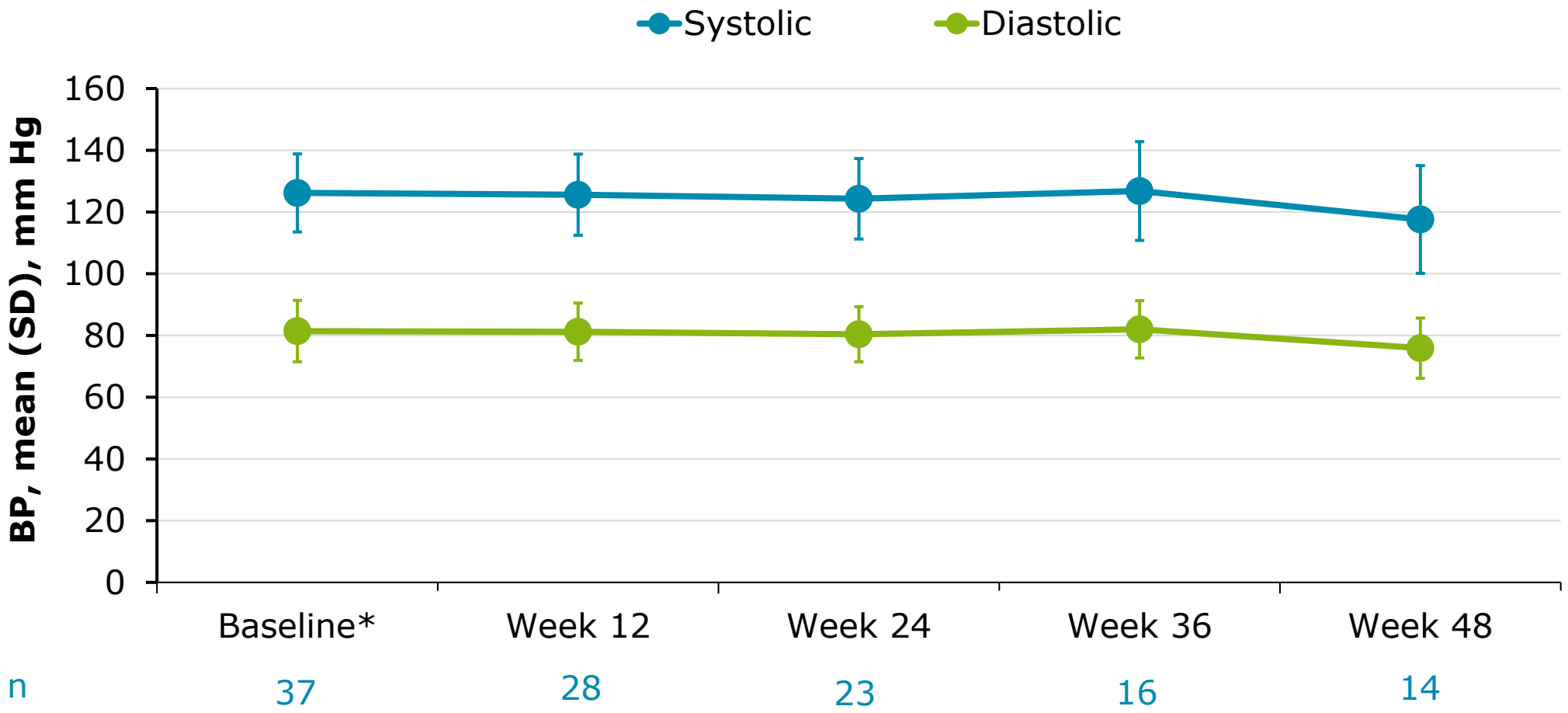
MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.
*TEAEs were based on MedDRA preferred terms.

# 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

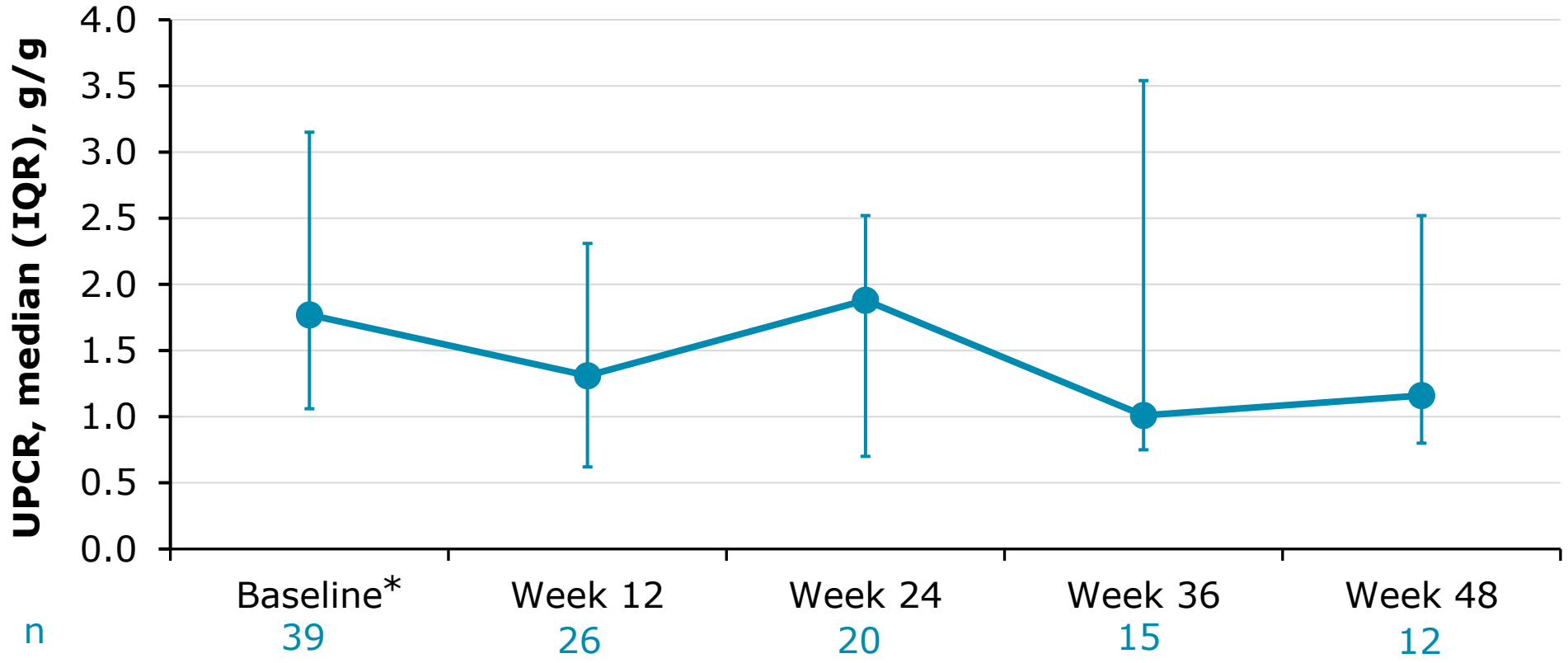



BP, blood pressure; OLE, open-label extension; SGLT2i, sodium-glucose cotransporter-2 inhibitor.
*Baseline was defined as the OLE visit closest to the SGLT2i start (ie, before or <14 days after start of SGLT2i treatment). Data are shown at weeks 12, 24, 36, and 48 after baseline.

# 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




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

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