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

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RESULTS

Patient Population

- At data cutoff, 61 patients had initiated concomitant SGLT2i on top of SPAR in the OLE period
  - 10 patients discontinued sparsentan and the OLE, including 4 who first discontinued SGLT2i treatment and then discontinued the OLE
    - SPAR discontinuations were due to adverse events (n=7), kidney transplant or dialysis (n=1), physician decision (n=1), and patient decision (n=1)
  - 7 patients discontinued SGLT2i treatment but are continuing to receive SPAR 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 at SGLT2i Baseline

Demographic parameters	Patients (N=61)
Sex, n (%)	
Male	43 (70)
Female	18 (30)
Race, n (%)	
White	43 (70)
Asian	13 (21)
Black/African American	2 (3)
Other	3 (5)
Ethnicity, n (%)	
Not Hispanic/Latino	59 (97)
Hispanic/Latino	2 (3)
Age at baseline visit, mean (SD), years	46.2 (11.7)

Table 2. Clinical Characteristics and Medication Use at SGLT2i Baseline

Parameters	Patients (N=61)
Clinical measurements	
BMI, mean (SD), kg/m^2	28.3 (4.8)*
Body weight, mean (SD), kg	87.4 (29.9)*
SBP, mean (SD), mm Hg	126.5 (11.9)*
DBP, mean (SD), mm Hg	80.9 (9.6)*
UPE, median (IQR), g/day	1.8 (1.0-3.2)
UPCR, median (IQR), g/g	1.3 (0.8-2.3)
eGFR, mean (SD), mL/min/1.73 m^2	41.8 (20.9)†
History of hypertension, n (%)	49 (80)
Antihypertensive medications at baseline visit, n (%)	40 (66)
Diuretics	21 (34)
β-Blockers	15 (25)
α-Blockers	7 (11)
Calcium channel blockers	26 (43)
Other	2 (3)
Time from start of OLE treatment to start of SGLT2i treatment, median (IQR), days	261.0 (148.0-411.0)

*n=59. †n=60.

Safety and Efficacy

- 46 patients (75%) had a TEAE and 7 patients (11%) had a serious TEAE (**Table 3**)
- There were no cases of Hy's Law reported (ALT or AST >3x ULN, with total bilirubin >2x ULN)
- Body weight (**Figure 1**) and blood pressure (systolic and diastolic; **Figure 2**) remained relatively stable over time following the addition of an SGLT2i to SPAR treatment
- Combination therapy of SPAR plus an SGLT2i led to a further reduction in proteinuria (**Figure 3**)
- eGFR levels over time are shown in **Figure 4**

Table 3. Summary of TEAEs

TEAEs*		Serious TEAEs*	
Patients	**N=61**	**Patients**	**N=61**
Patients with any TEAE, n (%)	46 (75)	**Patients with any serious TEAE, n (%)**	7 (11)
TEAEs in ≥5% of patients, n (%)		**All serious TEAEs, n (%)**	
Hyperkalemia	7 (11)	Hyperkalemia	2 (3)
COVID-19†	6 (10)	Abortion spontaneous	1 (2)
Hypertension	4 (7)	Acute kidney injury	1 (2)
Hypotension	4 (7)	Chronic kidney disease	1 (2)
Chronic kidney disease	3 (5)	COVID-19†	1 (2)
Cough	3 (5)	Headache	1 (2)
Glomerular filtration rate decreased	3 (5)	Small intestinal obstruction	1 (2)
Peripheral edema	3 (5)	Umbilical hernia	1 (2)
Upper respiratory tract infection	3 (5)		

*TEAEs were based on MedDRA preferred terms. †This study overlapped with the COVID-19 pandemic.

Figure 1. Body Weight Over Time

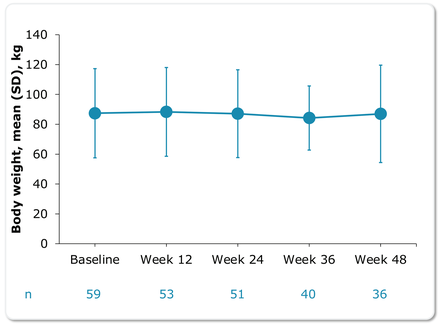


Figure 2. Systolic and Diastolic Blood Pressure Over Time

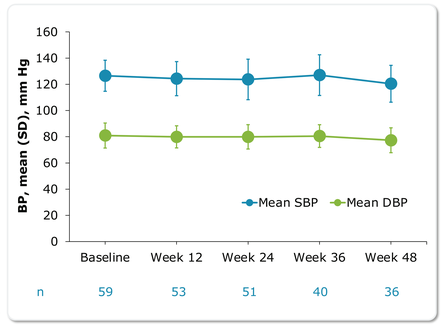


Figure 3. UPCR Over Time With SGLT2i Added to Stable SPAR Treatment

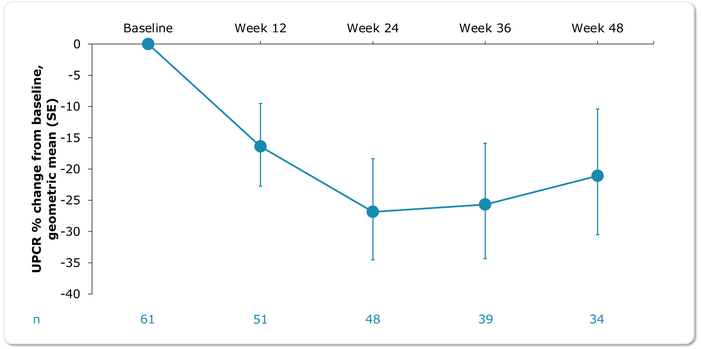
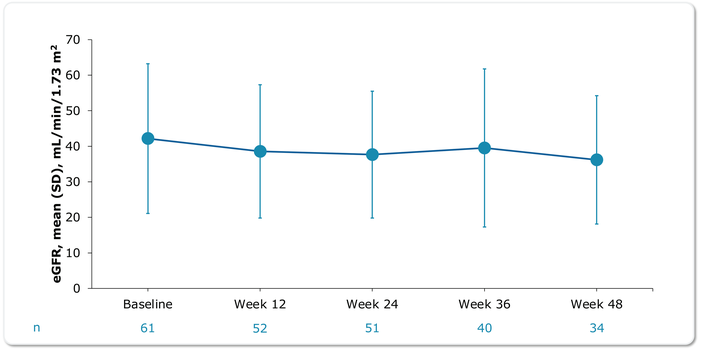


Figure 4. eGFR Over Time With SGLT2i Added to Stable SPAR Treatment



CONCLUSIONS

- Addition of an SGLT2i to stable SPAR treatment in patients with IgAN in the PROTECT OLE period was generally well tolerated. Stable weight and blood pressure were maintained
- Data are consistent with an additive benefit on proteinuria reduction with the addition of SGLT2i to stable SPAR
- Considering that the draft updated KDIGO guidelines recommend lower proteinuria targets and early combination treatment[9], SPAR in combination with SGLT2is represents an effective treatment with a good safety profile for patients with IgAN

ABBREVIATIONS

ACEi, angiotensin-converting-enzyme inhibitor; **ALT**, alanine aminotransferase; **ARB**, angiotensin II receptor blocker; **AST**, aspartate aminotransferase; **AT$_1$R**, angiotensin type 1 receptor; **BMI**, body mass index; **DAPA-CKD**, dapagliflozin and prevention of adverse outcomes in chronic kidney disease; **DB**, double-blind; **DBP**, diastolic blood pressure; **DEARA**, dual endothelin angiotensin receptor antagonist; **eGFR**, estimated glomerular filtration rate; **EMPA-KIDNEY**, empagliflozin in patients with chronic kidney disease; **ET$_A$R**, endothelin A receptor; **IgA**, immunoglobulin A; **IgAN**, IgA nephropathy; **IRB**, irbesartan; **MedDRA**, Medical Dictionary for Regulatory Activities; **OLE**, open-label extension; **SBP**, systolic blood pressure; **SGLT2i**, sodium-glucose cotransporter-2 inhibitor; **SOC**, standard of care; **SPAR**, sparsentan; **TEAE**, treatment-emergent adverse event; **ULN**, upper limit normal; **UPCR**, urine protein-to-creatinine ratio; **UPE**, urine protein excretion.

DISCLOSURES

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INTRODUCTION

BACKGROUND

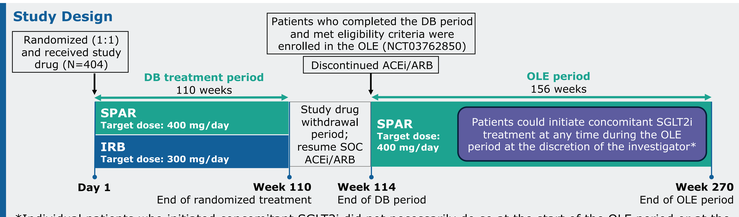
- SPAR is a novel, non-immunosuppressive, single-molecule DEARA with high selectivity for the ET$_A$R and AT$_1$R[1]
- In the PROTECT trial, SPAR demonstrated superior efficacy for proteinuria reduction and better preservation of kidney function vs maximum labeled dose irbesartan in patients with IgAN[2,3]
- SPAR is approved in the US and EU for adults with IgAN[4,5]
- Subgroup analyses from DAPA-CKD and EMPA-KIDNEY suggest that SGLT2is may reduce IgAN progression[6,7]
- In the PROTECT OLE, early clinical data showed that adding SGLT2i to ongoing SPAR was generally well tolerated and demonstrated a benefit on proteinuria reduction[8]

OBJECTIVE

- Here we report updated safety and efficacy data in patients within the PROTECT OLE who added concomitant SGLT2i treatment to their ongoing SPAR treatment

METHODS

Study Design



*Individual patients who initiated concomitant SGLT2i did not necessarily do so at the start of the OLE period or at the same time as each other. Patients may have received SPAR or IRB during the DB treatment period.

Analysis of Patients in the OLE Who Added SGLT2i to Their Ongoing SPAR Treatment:

Key Eligibility Criteria

- Enrollment and active participation in the PROTECT OLE period while continuing SPAR treatment
- Initiation of an SGLT2i as concomitant medication during the OLE period
- Patients were excluded if enrolled in the randomized PROTECT OLE SGLT2i substudy

Outcomes and Statistical Analysis Methods

- Body weight, SBP and DBP, and UPCR (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)
- TEAEs were determined
- Safety and efficacy endpoints were summarized using descriptive statistics for patients who received ≥1 dose of SPAR plus an SGLT2i

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