Sparsentan Reduces Proteinuria in Patients With Immunoglobulin A Nephropathy (IgAN): Interim Results of the Protect Study

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TRAVERE THERAPEUTICS

RESULTS

Patient Characteristics

- 671 patients were screened in 18 countries at 156 clinical practice sites; 406 were enrolled and randomly assigned to treatment with sparsentan or active control irbesartan
- Two randomized patients (one in each treatment group) did not receive study medication; 404 patients (202 randomized to sparsentan, 202 randomized to irbesartan) are included
- The median (IQR) duration of treatment at the efficacy data cutoff was 64.1 (30.1-94.4) weeks and at the safety data cutoff was 86.9 (48.9-110.0) weeks
- 189 (93.6%) patients receiving sparsentan and 194 (96.0%) receiving irbesartan increased to the target doses
- Baseline characteristics were well balanced between treatment groups (**Table 1**)

Table 1. Baseline Characteristics

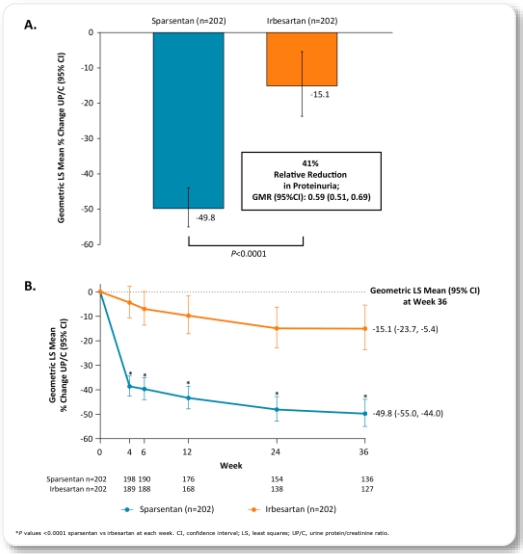
	Sparsentan N=202	Irbesartan N=202
Age at informed consent, years, mean±SD	47±13	45±12
Sex, n (%)		
Female	63 (31)	59 (29)
Race, n (%)[a]		
Asian	67 (33)	49 (24)
Black or African American	1 (<1)	3 (1)
White	130 (64)	142 (70)
Other	4 (2)	9 (4)
Not Hispanic or Latino[b]	185 (92)	186 (92)
Age at IgAN diagnosis, years, mean±SD	40±13	39±12
Time from initial kidney biopsy to informed consent, years, mean±SD	6±7	6±7
History of hypertension, n (%)	144 (71)	140 (69)
Blood pressure, mmHg, mean±SD		
Systolic	128±14	130±12
Diastolic	82±11	83±11
UP/C, g/g, median (IQR)	1.3 (0.8-1.8)	1.2 (0.9-1.7)
Urinary protein excretion, g/day, median (IQR)	1.8 (1.2-2.8)	1.8 (1.3-2.6)
eGFR, mean±SD[c]	57±24	57±24
eGFR category, n (%)		
≥90	26 (13)	25 (12)
≥60 to <90	49 (24)	48 (24)
≥45 to <60	45 (22)	49 (24)
≥30 to <45	67 (33)	75 (37)
≥15 to <30	15 (7)	5 (2)

[a]Patients may have selected more than one race. "Other" race included American Indian or Alaskan Native and Other. Native Hawaiian or Other Pacific Islander were combined with Asian to prevent inadvertent unblinding. [b]Not reported was combined with not Hispanic or Latino to prevent inadvertent unblinding. [c]eGFR was determined using the Chronic Kidney Disease Epidemiology formula and is given as mL/min/1.73 m². eGFR, estimated glomerular filtration rate; IQR, interquartile range; SD, standard deviation; UP/C, urine protein/creatinine ratio.

Efficacy

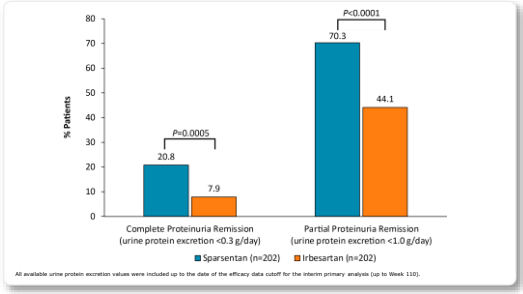
- At Week 36, the geometric least squares (LS) mean percent change from baseline in UP/C was significantly greater in the sparsentan group vs active control irbesartan (geometric LS mean ratio [sparsentan/ irbesartan]=0.59; 95% CI, 0.51-0.69; *P*<0.0001; **Figure 1A**)
- Reduction in UP/C was observed early in the sparsentan group, at Week 4, and was consistently significantly greater in the sparsentan group vs irbesartan (**Figure 1B**)
- Complete and partial remission of proteinuria at any time during the double-blind treatment period were greater in the sparsentan group vs irbesartan (**Figure 2**)
- The number of participants reaching a confirmed 40% reduction in eGFR from baseline, KF, or all-cause mortality was n=7 (3.5%) in the sparsentan group compared with n=13 (6.4%) in the irbesartan group

Figure 1. Percent change from baseline in UP/C (A) at Week 36 (primary efficacy endpoint) and (B) by visit



*P values <0.0001 sparsentan vs irbesartan at each week. CI, confidence interval; LS, least squares; UP/C, urine protein/creatinine ratio.

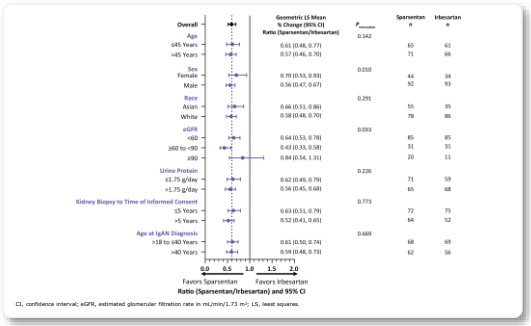
Figure 2. Percentage of patients achieving complete and partial remission of proteinuria



All available urine protein excretion values were included up to the date of the efficacy data cutoff for the interim primary analysis (up to Week 110).

- Proteinuria reduction with sparsentan vs active control irbesartan was consistent across baseline subgroups in demographic and clinical characteristics, including eGFR and urine protein excretion (**Figure 3**)

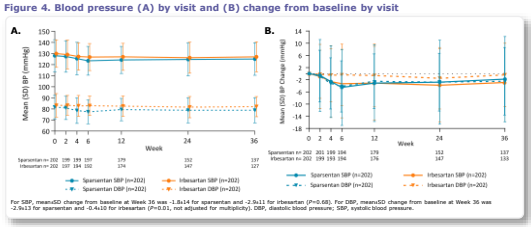
Figure 3. Subgroup analyses of percent change from baseline in UP/C at 36 weeks



CI, confidence interval; eGFR, estimated glomerular filtration rate in mL/min/1.73 m²; LS, least squares.

- Modest reduction in blood pressure occurred with sparsentan and irbesartan treatment, with minimal differences between treatment groups (**Figure 4**)

Figure 4. Blood pressure (A) by visit and (B) change from baseline by visit



For SBP, mean±SD change from baseline at Week 36 was -1.8±14 for sparsentan and -2.9±11 for irbesartan (P=0.68). For DBP, mean±SD change from baseline at Week 36 was -2.9±13 for sparsentan and -0.4±10 for irbesartan (P=0.01, not adjusted for multiplicity). DBP, diastolic blood pressure; SBP, systolic blood pressure.

Safety

- TEAEs are shown in **Table 2**
- Most peripheral edema TEAEs were rated as mild, and none were rated severe
- Investigators categorized peripheral edema as grade 3 or 4 in n=4 (2%) sparsentan-treated patients and n=8 (4%) irbesartan-treated patients
- Diuretics were initiated in a similar proportion of patients receiving sparsentan (18%) and irbesartan (19%), including loop diuretics (10% sparsentan-treated patients and 12% irbesartan-treated patients)
- There were no treatment-related fluid retention serious adverse events, cases of heart failure, or treatment discontinuations that were due to peripheral edema
- The frequency of liver enzyme elevations >3× ULN was low and comparable between sparsentan and irbesartan treatment groups; all occurred without concurrent elevation in total bilirubin and were asymptomatic and reversible

Table 2. Treatment-emergent adverse events

	Sparsentan N=202	Irbesartan N=202
Any TEAE, n (%)	177 (88)	158 (78)
TEAEs in ≥2% of participants treated with sparsentan, n (%)		
Peripheral edema (mostly mild, none severe)	29 (14)	19 (9)
Hypotension (including orthostatic hypotension)	28 (14)	12 (6)
Dizziness	27 (13)	11 (5)
Hyperkalemia	27 (13)	21 (10)
Anemia	10 (5)	5 (2)
Acute kidney injury (none occurred within 6 weeks of the start of study treatment; none required dialysis)[a]	9 (4)	2 (1)
Transaminase elevations >3× ULN (all without concurrent elevation in total bilirubin; all asymptomatic and reversible)	5 (2)	4 (2)

TEAEs in which sparsentan and irbesartan were similar (typically <3% difference), or irbesartan was greater, are not shown. [a]Acute kidney injury was typically reported based on changes in serum creatinine between study visits. All AKI cases rated as severe or serious were considered related to intercurrent illness (dehydration, infection), underlying disease progression, or preceding and/or concurrent condition rather than treatment-related. TEAEs, treatment-emergent adverse events; ULN, upper limit of normal.

- There were no discontinuations due to hyperkalemia in either treatment group
- There was 1 hyperkalemia serious AE in an irbesartan-treated patient and none in sparsentan-treated patients
- Mean potassium levels by study visit are shown in **Table 3**

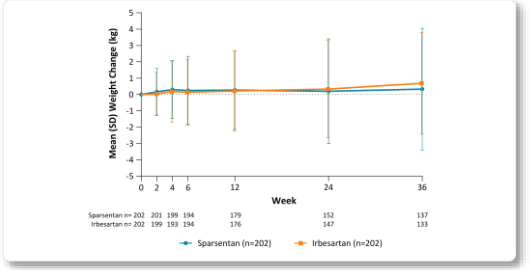
Table 3. Potassium levels by visit in the sparsentan and irbesartan groups

Study Visit	Sparsentan N=202	Irbesartan N=202
Potassium, mmol/L[a]		
Baseline	4.7±0.4	4.6±0.4
Week 4	4.7±0.4	4.6±0.4
Week 6	4.7±0.5	4.6±0.4
Week 12	4.6±0.4	4.6±0.4
Week 24	4.7±0.4	4.7±0.4
Week 36	4.7±0.4	4.7±0.5

Data are mean±SD. [a]The proportion of participants with a potassium level ≥6 mmol/L at any visit after baseline was 4% (8/202) in sparsentan-treated and 3% (6/202) in irbesartan-treated participants.

- Body weight changes from baseline were not different between the sparsentan and irbesartan groups (**Figure 5**)

Figure 5. Weight change from baseline in the sparsentan vs irbesartan treatment groups



CONCLUSIONS

- In adult patients with IgAN and persistent proteinuria above 1 g/day despite being treated with ACEis and/or ARBs, once-daily treatment with sparsentan compared head-to-head with active control irbesartan produced a rapid, sustained, and clinically meaningful reduction in proteinuria that was superior to treatment with irbesartan
- Sparsentan was well tolerated with a manageable safety profile
- There were no severe fluid retention adverse events, no treatment-related fluid retention serious adverse events, and no cases of heart failure
- The frequency of liver enzyme elevations >3× ULN was low and comparable between sparsentan treatment and irbesartan
- Future analyses of the ongoing PROTECT study will examine long-term efficacy and safety of sparsentan in patients with IgAN, to be conducted after the completion of the 2-year double-blind period

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INTRODUCTION

- IgAN is the most common glomerular disease worldwide and a significant cause of kidney failure (KF) despite optimized standard of care[1,2]
- Proteinuria is a modifiable risk factor for progressive kidney function loss in patients with IgAN, and proteinuria remission is associated with improved kidney outcomes[3,4]
- Novel treatments that produce greater proteinuria reduction and reduce risk of kidney disease progression are urgently needed for IgAN
- Sparsentan, a novel, nonimmunosuppressive, single molecule that is a dual endothelin angiotensin receptor antagonist (DEARA), recently received approval by the US Food and Drug Administration for the reduction of proteinuria in adults with IgAN at high risk of disease progression
- The phase 3 PROTECT study is examining the long-term antiproteinuric and nephroprotective potential and safety of sparsentan in a head-to-head comparison with maximum labeled or tolerated active control irbesartan, an angiotensin receptor blocker (ARB), in adults with IgAN[5,6]

Objective

- To report the ongoing PROTECT study prespecified interim primary efficacy endpoint and safety outcomes

METHODS

Study Design

- PROTECT is an ongoing, global, phase 3, multicenter, randomized, double-blind, active-controlled study designed to evaluate the efficacy and safety of sparsentan versus the active control irbesartan in adults with IgAN with overt proteinuria despite receiving maximized treatment with an angiotensin converting enzyme inhibitor (ACEi) and/or ARB[5]
- The study duration is 270 weeks; the double-blind period is 114 weeks (110 treatment and 4 follow-up) with an open-label extension period up to 156 weeks
- Patients took their last ACEi and/or ARB dose the day before randomization
- Patients were randomized 1:1 to sparsentan or irbesartan (target dose 400 and 300 mg/day, respectively), stratified by screening eGFR and urine protein excretion values

Participant Eligibility

- Adult patients eligible for inclusion had biopsy-proven IgAN (excluding IgAN secondary to another condition or IgA vasculitis), urine protein excretion value ≥1.0 g/day, eGFR ≥30 mL/min/1.73 m², systolic/diastolic blood pressure ≤150/≤100 mmHg, and were on a stable dose of ACEi and/or ARB therapy for at least 12 weeks prior to screening that was both the patient's maximum tolerated dose and at least one-half of the maximum labeled dose
- Aggregated baseline characteristics of the patients enrolled in PROTECT have been reported[6]

Endpoints

- Primary efficacy endpoint (prespecified interim analysis) is change from baseline in urine protein/creatinine ratio (UP/C, based on a 24-hour urine sample) at Week 36
  - Also examined by participant subgroups based on baseline demographic and clinical characteristics
- Other secondary efficacy endpoint: Proportion of patients reaching a confirmed 40% reduction in eGFR from baseline, KF, or all-cause mortality (KF is defined as initiation of kidney replacement therapy [KRT] or sustained eGFR value of <15 mL/min/1.73 m²)
- Exploratory endpoints included complete (urine protein excretion <0.3 g/day) and partial (urine protein excretion <1.0 g/day)[4] proteinuria remission at any time during the double-blind period
- Safety assessed treatment-emergent adverse events (TEAEs), prespecified liver function testing AEs of interest (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST] increase >3× the upper limit of normal [ULN] with or without elevation of total serum bilirubin >2× ULN), severity of edema via investigator semiquantitative ratings (Grades 0 to 4), and changes from baseline in body weight and blood pressure

Statistical Analysis

- The primary analysis set was used for all analyses: all patients who were randomized and received at least one dose of randomized treatment
- A mixed model repeated measures (MMRM) analysis with multiple imputation was used to evaluate change from baseline to Week 36 in UP/C (and in subgroups; efficacy data cutoff August 1, 2021)
- Logistic regression examined the proportion of patients achieving complete and partial proteinuria remission at any time over the course of the double-blind period
- Safety outcomes were examined descriptively (safety data cutoff February 1, 2022)

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