Implications of Proteinuria Remission on Estimated Glomerular Filtration Rate Trajectory in Patients With IgA Nephropathy in PROTECT

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RESULTS

Proteinuria Remission Rates in PROTECT

- Of 404 patients who were randomized and received either sparsentan or irbesartan:
  - 85 (21.0%) patients achieved CR at any time through Week 110 and 319 (79.0%) never achieved CR
  - 151 (37.4%) patients achieved UPE <0.5 g/d at any time through Week 110 and 253 (62.6%) did not

Demographics and Baseline Characteristics

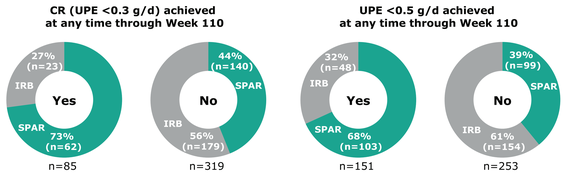
- While baseline age, sex, and race were similar for patients who achieved proteinuria remission vs those who did not, baseline UPE was lower and eGFR higher in the patients who achieved remission (**Table 1**)
- Most patients who achieved proteinuria remission had been randomized to sparsentan and the majority who did not had been randomized to irbesartan (**Figure 3**)

Table 1. Demographics and Baseline Characteristics by Proteinuria Remission Status*

Demographics and baseline characteristics	CR (UPE <0.3 g/d) achieved at any time through Week 110		UPE <0.5 g/d achieved at any time through Week 110	
	Yes (n=85)	No (n=319)	Yes (n=151)	No (n=253)
Age, mean (SD), y	44.3 (13.76)	46.5 (12.04)	45.1 (13.17)	46.5 (11.98)
Sex, male, n (%)	54 (64)	228 (71)	99 (66)	183 (72)
Race, n (%)				
American Indian or Alaskan native	0 (0)	0 (0)	0 (0)	0 (0)
Asian	29 (34)	86 (27)	49 (32)	66 (26)
Black or African American	1 (1)	3 (1)	1 (1)	3 (1)
Native Hawaiian/Other Pacific Islander	0 (0)	1 (<1)	0 (0)	1 (<1)
White	53 (62)	219 (69)	97 (64)	175 (69)
Other	2 (2)	11 (3)	4 (3)	9 (4)
UPE, median (IQR), g/d	1.27 (0.97-1.86)	2.01 (1.40-2.95)	1.43 (1.03-2.24)	2.03 (1.44-3.01)
UPCR, median (IQR), g/g	0.92 (0.66-1.17)	1.34 (0.91-1.86)	1.01 (0.67-1.47)	1.36 (0.94-1.92)
eGFR, mean (SD), mL/min/1.73 m²	65.1 (26.46)	54.8 (22.76)	60.3 (24.98)	54.9 (23.09)
Blood pressure, mean (SD), mm Hg				
SBP	128.2 (14.76)	129.2 (13.11)	127.1 (14.60)	130.1 (12.63)
DBP	80.9 (11.14)	82.9 (10.45)	81.0 (10.97)	83.3 (10.33)

*Data are for the full analysis set.

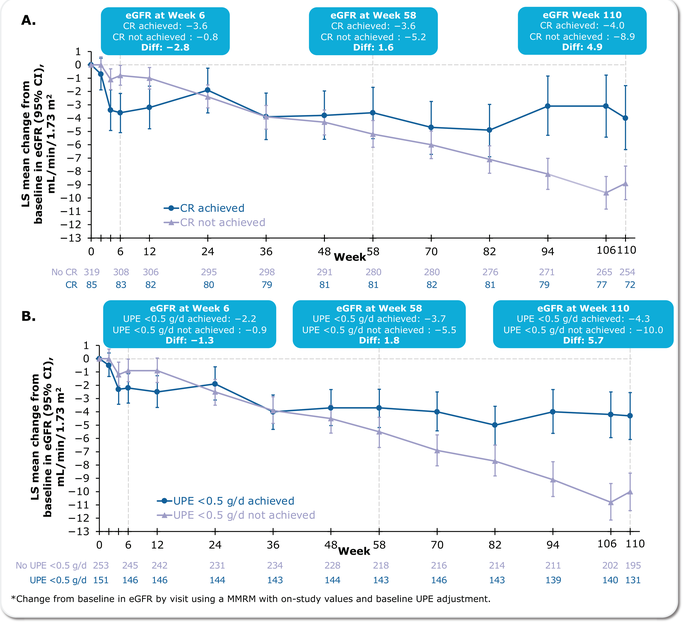
Figure 3. Patients Achieving or Not Achieving CR or UPE <0.5 g/d by Treatment Assignment



Absolute Change in eGFR From Baseline

- In patients who achieved CR or UPE <0.5 g/d at any time through Week 110, eGFR showed an acute drop in the first few weeks after which it remained relatively stable though Week 110 (**Figure 4**). In contrast, eGFR showed a smaller acute drop in patients who never achieved CR or UPE <0.5 g/d, after which it steadily declined through Week 110

Figure 4. Absolute Change From Baseline in eGFR at Each Study Visit in Patients Who Did or Did Not Achieve A) CR and B) UPE <0.5 g/d*



*Change from baseline in eGFR by visit using a MMRM with on-study values and baseline UPE adjustment.

Total and Chronic eGFR Slopes

- eGFR declined over time at a slower rate in patients who achieved CR or UPE <0.5 g/d at any time through Week 110 vs those who did not (**Table 2**)

Table 2. Total and Chronic eGFR Slopes*,†

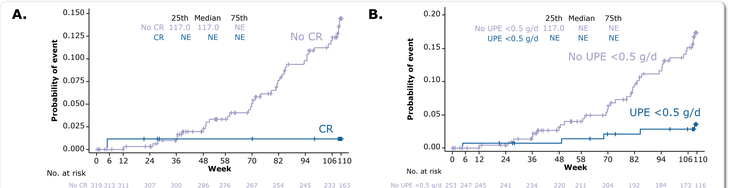
eGFR slope, mL/min/1.73 m²/y	CR (UPE <0.3 g/d) achieved at any time through Week 110		UPE <0.5 g/d achieved at any time through Week 110	
	Yes (n=85)	No (n=319)	Yes (n=151)	No (n=253)
Chronic slope, (95% CI) (Week 6 to Week 110)	−0.3 (−1.30 to 0.69)	−4.4 (−4.94 to −3.89)	−1.1 (−1.82 to −0.37)	−5.1 (−5.65 to −4.49)
Difference (95% CI; *P* value)	4.1 (2.98 to 5.23; <.0001)		4.0 (3.04 to 4.91; <.0001)	
Total slope, (95% CI)‡ (Day 1 to Week 110)	−1.0 (−1.94 to 0.03)	−4.5 (−5.00 to −3.96)	−1.6 (−2.31 to −0.87)	−5.1 (−5.64 to −4.49)
Difference (95% CI; *P* value)	3.5 (2.41 to 4.63; <.0001)		3.5 (2.55 to 4.40; <.0001)	

*Based on on-study data.
†eGFR slopes were assessed using linear mixed effects model and adjusted for baseline log transformed UPE.
‡Baseline (Day 1) eGFR is included as a response variable and covariate.

Composite KF Endpoint

- Markedly fewer patients who achieved CR or UPE <0.5 g/d reached the composite KF endpoint (1 [1.2%] and 6 [4.0%], respectively) compared with those who never achieved these endpoints (43 [13.5%] and 38 [15.0%], respectively) (**Figure 5**)

Figure 5. Kaplan-Meier Plot for Time to Reach the Composite KF Endpoint in Patients Who Achieved A) CR or B) UPE <0.5 g/d at Any Time Through Week 110*



*The composite KF endpoint was defined as confirmed 40% eGFR decline, end-stage kidney disease (initiation of renal replacement therapy or sustained eGFR <15 mL/min/1.73 m²), or mortality due to any cause.

Safety (CR Only)

- TEAEs occurred in 79 (93%) patients who achieved CR vs 285 (89%) who did not achieve CR at any time through Week 110
- The most common TEAEs were COVID-19, headache, hyperkalemia, edema peripheral, dizziness, hypotension, and hypertension
- TEAEs of interest (hypotension-, fluid retention-, anemia-, or hyperkalemia-associated) were comparable between groups

CONCLUSIONS

In patients with IgAN, achievement of low proteinuria is strongly predictive of better long-term kidney function

eGFR preservation was more evident in patients who achieved low proteinuria vs those who did not. Notably, in patients who achieved CR, the mean rate of kidney function decline (eGFR chronic slope) was below the therapeutic goal of <1.0 mL/min/1.73 m²/y

Substantially fewer patients who achieved CR or UPE <0.5 g/d reached the composite kidney failure endpoint than patients who did not

As sparsentan-treated patients achieved proteinuria remission more frequently vs maximum labeled dose irbesartan in the PROTECT trial, this analysis further supports the interplay between proteinuria and kidney function decline, and the benefit of sparsentan for long-term preservation of kidney function

ABBREVIATIONS

ACEi, angiotensin converting enzyme inhibitor; **ARB,** angiotensin receptor blocker; **CR,** complete proteinuria remission; **DEARA,** dual endothelin angiotensin receptor antagonist; **DBP,** diastolic blood pressure; **EU,** Europe; **eGFR,** estimated glomerular filtration rate; **IgAN,** IgA nephropathy; **IRB,** irbesartan; **KF,** kidney failure; **LS,** least squares; **MMRM,** mixed model repeated measures; **SBP,** systolic blood pressure; **SOC,** standard of care; **SPAR,** sparsentan; **TEAE,** treatment-emergent adverse event; **UPCR,** urine protein-to-creatinine ratio; **UPE,** urine protein excretion; **US,** United States.

DISCLOSURES

HJLH reports consultancy fees or grants from AstraZeneca, Bayer, Boehringer Ingleheim, Chinook, CSL Behring, Eli Lilly, Gilead, Janssen, Novartis, Novo Nordisk AS, and Travere Therapeutics, Inc. **VT** reports consultancy fees or honoraria from AstraZeneca, Bayer, Boehringer-Ingelheim, Calliditas, GSK, Eli Lilly, Novartis, Otsuka, Travere, Vera; and is a member of the steering committees of clinical trials sponsored by Calliditas, Novartis, Otsuka, Travere, Vera. **BR** reports consulting fees from Alexion Pharmaceuticals, Alpine Pharma, BioCryst Pharmaceuticals, Calliditas Therapeutics, Novartis, Q32 Bio, Omeros, Otsuka Pharmaceuticals, Travere Therapeutics, Inc., and Vera Therapeutics and has a leadership role at NephroNet, Lupus ABC/LRA, and Lupus Foundation of America. **RK, BH,** and **EM** are employees and stockholders of Travere Therapeutics, Inc. **PP** reports consultancy fees from, and is a stockholder and former employee of, Travere Therapeutics, Inc.

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INTRODUCTION

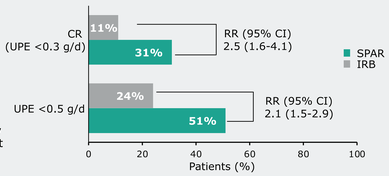
BACKGROUND

- Sparsentan, a non-immunosuppressive, dual endothelin angiotensin receptor antagonist (DEARA), is approved in the US and the EU for patients with IgAN based on 2-year data from the Phase 3 PROTECT trial[1-3]
- In PROTECT, sparsentan reduced proteinuria and increased the proportion of patients achieving CR (UPE <0.3 g/d) or UPE <0.5 g/d vs maximum labeled dose irbesartan (**Figure 1**)[3]
- In IgAN, proteinuria is significantly associated with worse kidney outcomes, and its reduction has been shown to predict slower disease progression and lower risk of kidney failure[4,5]

OBJECTIVE

- Determine the eGFR trajectories for patients who achieved CR or UPE <0.5 g/d at any time through Week 110 during the PROTECT trial vs those who did not (in a treatment agnostic analysis), to establish whether these levels of proteinuria reduction were associated with favorable outcomes

Figure 1. Patients Achieving CR or UPE <0.5 g/d in PROTECT[3]

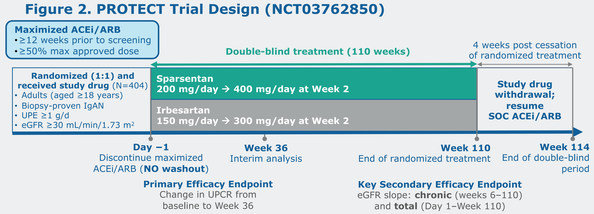


METHODS

Study Design

- PROTECT was a double-blind, randomized, active-controlled, Phase 3 study in patients with biopsy-proven IgAN (**Figure 2**)
- Patients were randomized (1:1) to receive sparsentan (400 mg once daily) or maximum labeled and tolerated dose irbesartan (target: 300 mg once daily) for up to 110 weeks

Figure 2. PROTECT Trial Design (NCT03762850)



Analysis Methods

- This *post hoc* analysis compared the rate of kidney function decline during 110-week follow-up, regardless of treatment allocation at randomization, in:
  - Patients who achieved CR vs those who did not
  - Patients who achieved UPE <0.5 g/d vs those who did not
- Outcomes assessed included:
  - Absolute change from baseline in eGFR (MMRM)
  - Chronic/total eGFR slope (mixed model random coefficients)
  - Proportion of patients achieving a composite kidney failure endpoint (Cox proportional hazards [regression] model)
  - Safety

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