Sparsentan Receptor Occupancy Modeling, Clinical Actions, and Safety

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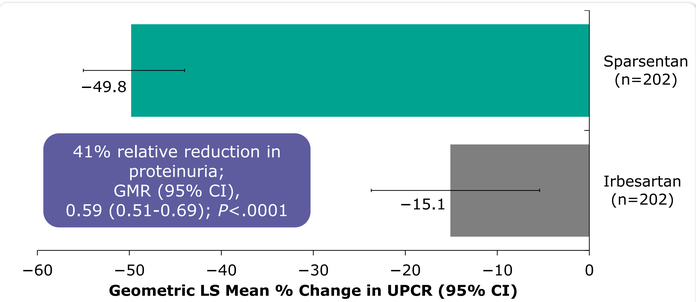
RESULTS

In PROTECT, sparsentan reduced proteinuria vs active comparator in patients with IgAN with minimal changes in fluid status[1,6]

- At week 36, the percent reduction in UPCR from baseline was significantly greater with sparsentan compared with irbesartan (**Figure 1**)

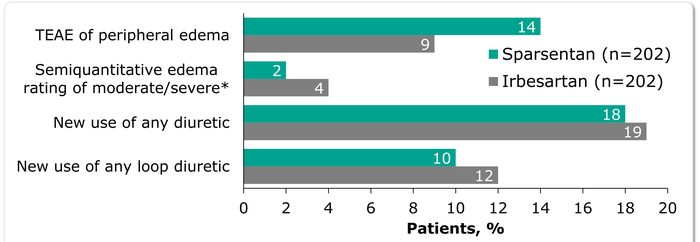
Figure 1. Percent Change in UPCR* From Baseline With Sparsentan vs Irbesartan at Week 36 in PROTECT[1]



GMR, geometric mean ratio; LS, least squares; UPCR, urine protein-to-creatinine ratio.
*UPCR is based on 24-hour urine samples.

- The incidence of TEAEs of peripheral edema was slightly higher with sparsentan but still low overall (**Figure 2**). Most cases of edema were mild, and no cases of severe edema occurred. There were no treatment-related fluid retention serious AEs or cases of heart failure
- Diuretics were initiated in a similar proportion of participants receiving sparsentan and irbesartan (**Figure 2**)
- These findings were consistent with results from the phase 3 DUPLEX trial in focal segmental glomerulosclerosis where no serious cases of peripheral edema were reported with sparsentan[7]

Figure 2. Peripheral Edema and Diuretic Use in PROTECT[1,6]



TEAE, treatment-emergent adverse event.
*The severity of edema was assessed by investigators at each visit using a semiquantitative scale adapted from the Guelph General Hospital Congestive Heart Failure Pathway (grades 0-4).

AT_1R occupancy always exceeds ET_AR occupancy with sparsentan

- Sparsentan human receptor affinities are reported in **Table 1**
- Steady-state PK parameters calculated using population PK values for sparsentan 400 mg in the PROTECT study are reported in **Table 2**
- Examining the full 24-hour period, sparsentan AT_1R occupancy (>95%) consistently exceeds ET_AR occupancy (>60% and <90%) (**Figure 3**)
- Examining the full 24-hour period, sparsentan ET_AR occupancy (>60% and <90%) consistently exceeds ET_BR occupancy (<2%) (**Figure 4**)

Table 1. Sparsentan Endothelin and Angiotensin Receptor Affinities

Receptor target	
Ki for AT_1R, nM	0.36
Ki for AT_2R, nM	190
Ki for ET_AR, nM	12.8
Ki for ET_BR, nM	6582
Protein binding, %	99

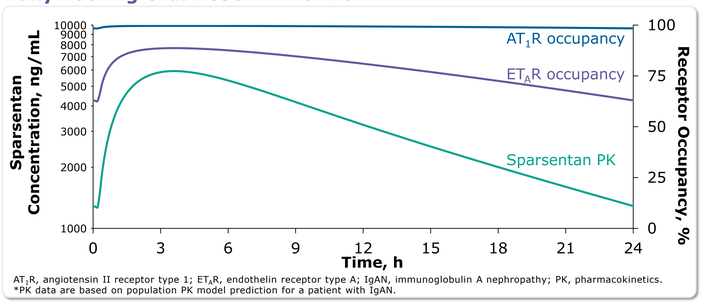
AT_1R, angiotensin II receptor type 1; AT_2R, angiotensin II receptor type 2; ET_AR, endothelin receptor type A; ET_BR, endothelin receptor type B; Ki, inhibitory constant.

Table 2. Sparsentan PK at Steady State

Steady-state parameter*	
C_{max}, ng/mL	5936
C_{min}, ng/mL	1266
$t_{½}$, hours	9.6
AUC, ng·h/mL	80000

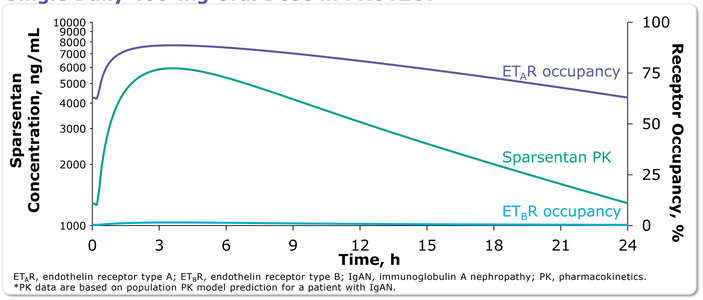
AUC, area under the curve; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; IgAN, immunoglobulin A nephropathy; PK, pharmacokinetics; $t_{½}$, half-life.
*PK data were based on population PK model prediction for a patient with IgAN.

Figure 3. Sparsentan AT_1R and ET_AR Occupancies (Right Axis) and Steady-State Concentration* (Left Axis) Over 24 Hours for a Single Daily 400-mg Oral Dose in PROTECT



AT_1R, angiotensin II receptor type 1; ET_AR, endothelin receptor type A; IgAN, immunoglobulin A nephropathy; PK, pharmacokinetics.
*PK data are based on population PK model prediction for a patient with IgAN.

Figure 4. Sparsentan ET_AR and ET_BR Occupancies (Right Axis) and Steady-State Concentration* (Left Axis) Over 24 Hours for a Single Daily 400-mg Oral Dose in PROTECT



ET_AR, endothelin receptor type A; ET_BR, endothelin receptor type B; IgAN, immunoglobulin A nephropathy; PK, pharmacokinetics.
*PK data are based on population PK model prediction for a patient with IgAN.

INTRODUCTION

- In the PROTECT study, sparsentan, which targets both the endothelin receptor type A (ET_AR) and angiotensin II receptor type 1 (AT_1R), reduced proteinuria vs active comparator in patients with immunoglobulin A nephropathy (IgAN) with minimal changes in fluid status[1]
- This contrasts with greater fluid retention, including heart failure hospitalization, in studies using agents targeting ET_AR alone.[2-4] This may relate to differences in comorbidities; however, aspects of dual receptor binding by sparsentan may also be a factor
- Since ET_AR blockers favor fluid retention[5] while AT_1R blockers may promote fluid excretion, continual consistent blockade of AT_1R during ET_AR blockade may help maintain normal fluid balance
- The pharmacokinetic (PK) properties of sparsentan were used to estimate diurnal changes in receptor occupancy at steady state in the PROTECT study

METHODS

- PROTECT (NCT03762850) is an international, randomized, double-blind, active-controlled study being conducted in 134 clinical practice sites in 18 countries
- The study examines sparsentan vs irbesartan in adults (aged ≥18 years) with biopsy-proven IgAN who had proteinuria of ≥1.0 g/day despite maximized renin-angiotensin-system inhibition for ≥12 weeks
- Participants were randomly assigned 1:1 to receive sparsentan, 400 mg once daily, or irbesartan, 300 mg once daily, stratified by estimated glomerular filtration rate (eGFR) at screening (30 to <60 vs ≈60 mL/min/1.73 m^2) and urine protein excretion at screening (≤1.75 vs >1.75 g/day)
- The primary efficacy endpoint was change in urine protein-to-creatinine ratio (UPCR), based on a 24-hour urine sample, from baseline to week 36 assessed using a mixed model for repeated measures
- Treatment-emergent adverse events (TEAEs) were safety endpoints
- All endpoints were examined in all participants who received ≥1 dose of randomized treatment
- Receptor affinities (inhibitory constant [Ki]) of sparsentan for ET_AR, endothelin receptor type B (ET_BR), AT_1R, and angiotensin II receptor type 2 (AT_2R) were determined using radioligand binding assays
- Population PK modeling of sparsentan was used to derive 24-hour PK and receptor occupancy profiles of patients in PROTECT

DISCUSSION

- Sparsentan exhibits strong antiproteinuric efficacy without associated clinically significant fluid overload events[1]
- We hypothesize that this arises from the properties of sparsentan as a dual endothelin angiotensin receptor antagonist (DEARA)[8–10]
- When a drug solely targets ET_AR, on top of AT_1R blockade, periods of relatively unaccompanied ET_AR antagonism may occur, representing a risk for fluid retention. If AT_1R blockade consistently exceeds ET_AR antagonism, then this risk is minimized or avoided
- The presented receptor occupancy data from PROTECT are consistent with this hypothesis, showing that with sparsentan, ET_AR antagonism is substantial and always accompanied by full AT_1R occupancy

CONCLUSIONS

- AT_1R occupancy always exceeds ET_AR occupancy with sparsentan; ET_BR occupancy with sparsentan is negligible
- In contrast, when a drug solely targets ET_AR, on top of AT_1R blockade, periods of relatively unaccompanied ET_AR antagonism may occur, representing a risk for fluid retention
- This could partly explain the fluid retention seen with endothelin receptor antagonists and the minimal changes in fluid status seen with sparsentan

DISCLOSURES

BH, **RG**, **CJ**, **S-CC**, and **PWB** are employees of Travere Therapeutics, Inc., and may have equity or other financial interest in Travere Therapeutics, Inc. **DK** received consulting fees from AstraZeneca, Chinook Therapeutics, and Travere Therapeutics, Inc. and honoraria from Chinook Therapeutics and Travere Therapeutics, Inc.

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