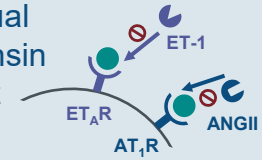
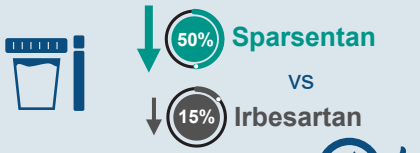
Sparsentan Receptor Occupancy Modeling, Clinical Actions, and Safety

Background

Sparsentan is a dual endothelin angiotensin receptor antagonist (DEARA)[1-3]



In the PROTECT trial, sparsentan led to a greater reduction in proteinuria vs active comparator[4]

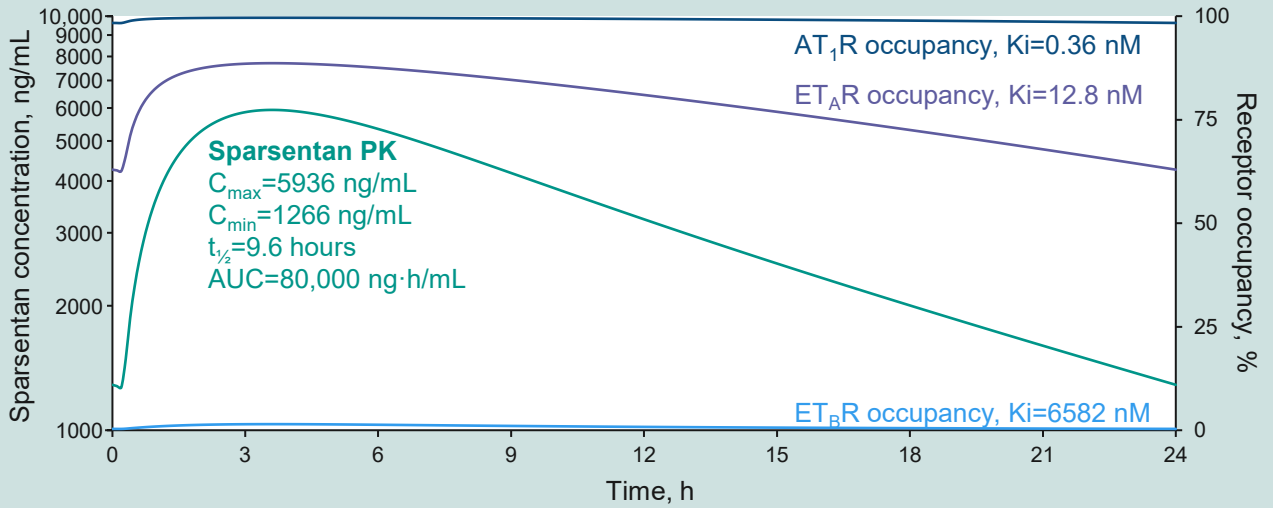


With minimal changes in fluid status[4]

Objective

To estimate receptor occupancy using steady state pharmacokinetics (PK) of sparsentan from patients with IgAN in the PROTECT trial

Sparsentan steady state PK and receptor occupancies over 24 hours following 400 mg oral dose in PROTECT*



- Over 24-h period, AT_1R occupancy always exceeds ET_AR occupancy with sparsentan
- Over 24-h period, ET_AR occupancy always exceeds ET_BR occupancy, which is negligible with sparsentan

Methods

In the PROTECT trial, patients were randomized 1:1

Sparsentan 400 mg/day

Irbesartan 300 mg/day

PROTECT eligibility criteria

- Adults (age ≥18 years)
- Biopsy-proven IgAN
- Proteinuria ≥1.0 g/day, despite maximum RAS inhibition for ≥12 weeks
- eGFR ≥30 mL/min/1.73 m^2

Primary efficacy endpoint was change in UPCR based on a 24-h urine sample

Receptor affinities were determined using radioligand binding assays

Population PK modeling was used to derive the 24-h PK and receptor occupancy profiles

Conclusions

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, the risk of fluid retention is minimized or avoided. This could partly explain the fluid retention seen with single-target endothelin receptor antagonists and the minimal change in fluid status seen with DEARA sparsentan

ANGII, angiotensin II; AT_1R, angiotensin receptor type 1; AUC, area under the curve; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; eGFR, estimated glomerular filtration rate; ET-1, endothelin 1; ET_AR, endothelin receptor type A; ET_BR, endothelin receptor type B; IgAN, immunoglobulin A nephropathy; PK, pharmacokinetics; RAS, renin-angiotensin system; $t_{½}$, half life; UPCR, urine protein-to-creatinine ratio. *PK data are based on population PK model prediction for patients with IgAN.

1. Trachtman H, et al. *Expert Opin Emerg Drugs*. 2020;25(3):367-375. 2. Kowala MC, et al. *J Pharmacol Exp Ther*. 2004;309(1):275-284. 3. Nagasawa H, et al. *Nephrol Dial Transplant*. 2022;37:183. 4. Heerspink HJL, et al. *Lancet*. 2023;13;401(10388):1584-1594.

Hendry B, et al. ASN Kidney Week 2023
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