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Title: Sparsentan receptor occupancy modeling, clinical actions, and safety

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Introduction 822: In the PROTECT study, sparsentan, which targets both the endothelin type A (ET_AR) and angiotensin type 1 (AT_1R) receptors, reduced proteinuria vs active comparator in IgA nephropathy with minimal changes in fluid status. This contrasts with greater fluid retention, including heart failure hospitalization, in studies using agents targeting ET_AR alone (ERA). 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 while AT_1R blockers may promote fluid excretion, continual high 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 (RO) at steady state in the PROTECT study.

Methods 211: Receptor affinities (Ki) were determined for sparsentan at ET_AR, ET_BR, and AT_1R using radioligand binding assays. PopPK modeling of sparsentan was used to derive 24-hour PK and RO profile of patients in PROTECT.

Results 281: Sparsentan receptor affinities and PK data of a typical IgAN patient in PROTECT study are shown in Fig. 1A. The 24-hour plot of sparsentan RO for ET_AR, ET_BR, and AT_1R using PK data estimated for 400 mg daily, shows RO is ~60-90% for ET_AR, >95% for AT_1R, and <1% for ET_BR (Fig. 1B).

Conclusions 413: Sparsentan has a stable 24-hour relationship in relative RO of ET_AR to AT_1R in which AT_1R RO always exceeds ET_AR RO. 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 ERA and the minimal changes in fluid status seen with sparsentan.

Category: Pharmacology

Keywords: Pharmacokinetics, IgA nephropathy

Title 269 Fig 1: (A) Sparsentan receptor binding parameters and steady-state mean PK estimates from the PROTECT study. (B) Sparsentan receptor occupancies (right axis) over 24 hours for a single daily 400 mg oral dose in the PROTECT study, steady-state mean exposure (left axis).

(A)

Parameter	Value	Steady State Parameter	Value
Ki (ET_AR)	12.8 nM	Cmax	6470 ng/ml
Ki (AT_1R)	0.36 nM	Cmin	1266 ng/ml
Ki (ET_BR)	6582 nM	Half-life	9.6 hours
Protein binding	99%	AUC	63,600 ng.hr/ml

(B)