The Effect of an Acid-Reducing Agent, Esomeprazole, on Sparsentan Pharmacokinetics in Healthy Volunteers

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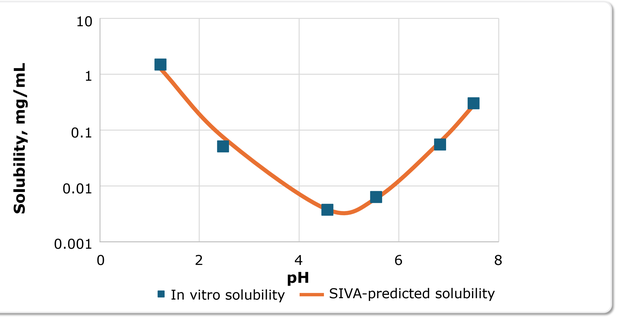
DATA AND RESULTS

Sparsentan's Solubility Profile

- The solubility modeling results within SIVA, along with the in vitro pH solubility assay, demonstrated that sparsentan exhibits pH-dependent solubility, with solubility decreasing as pH increases from 1 to 5 (**Figure 2**)

Figure 2. Sparsentan's pH-Dependent Solubility Profile



- The PBPK pH sensitivity analysis predicted that increasing the stomach pH from 1.5 to 5 led to a reduction of 37.1% in the geometric mean value of sparsentan's C_{max} and a 32.5% reduction in its $AUC_{0\text{-}inf}$ (**Table 1**)

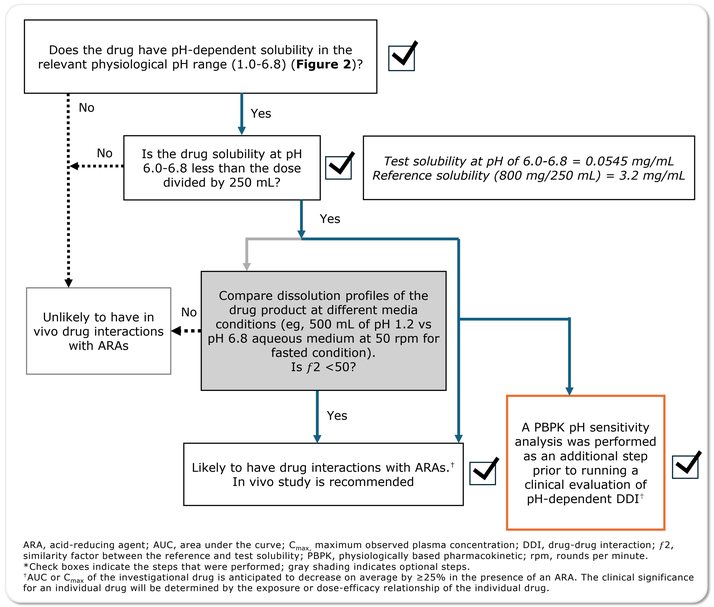
Table 1. PBPK pH Sensitivity Analysis - Summary of Sparsentan's PK Profile*

Prandial state	C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (ng/mL·h)	T_{max} (h)	fa
Fasted stomach pH (1.5)	8,755	143,091	2.09	0.26
Fasted stomach pH (5.0)	5,509	96,546	3.85	0.18
Fasted (pH, 5)/fasted (pH, 1.5)†	0.6292	0.6747		

$AUC_{0\text{-}inf}$, area under the concentration time curve from time 0 extrapolated to infinity; C_{max}, maximum observed plasma concentration; fa, fraction absorbed; PK, pharmacokinetic; T_{max}, time to reach C_{max}.
*Data are presented as geometric mean values. †The ratio of PK exposure parameters (C_{max} and $AUC_{0\text{-}inf}$) under fasted conditions at pH 5 compared to pH 1.5.

- The US Food and Drug Administration recommendations[5] for assessing clinical DDI risk with ARAs, which were used to evaluate the potential of pH-dependent DDI when sparsentan is combined with ARAs, are presented in **Figure 3**

Figure 3. A Framework to Assess Clinical DDI Risk With ARAs*



ARA, acid-reducing agent; AUC, area under the curve; C_{max}, maximum observed plasma concentration; DDI, drug-drug interaction; ƒ2, similarity factor between the reference and test solubility; PBPK, physiologically based pharmacokinetic; rpm, rounds per minute.
*Check boxes indicate the steps that were performed; gray shading indicates optional steps.
†AUC or C_{max} of the investigational drug is anticipated to decrease on average by ≥25% in the presence of an ARA. The clinical significance for an individual drug will be determined by the exposure or dose-efficacy relationship of the individual drug.

Clinical Study Results

- The phase 1 clinical study results indicated that the PK exposure metrics (AUC and C_{max}) for sparsentan were comparable when administered alone and in combination with esomeprazole (**Table 2**)
- The 90% CI of the ratio of GeoLSM of C_{max}, $AUC_{0\text{-}24}$, and $AUC_{0\text{-}inf}$ between the 2 treatments fell within 80% and 125% (**Table 3**)

Table 2. Plasma Sparsentan PK Parameters Following Esomeprazole 40 mg + Sparsentan 800 mg Versus Sparsentan 800 mg Alone*

Dependent	Unit	Esomeprazole + sparsentan	Sparsentan alone
$AUC_{0\text{-}inf}$ (SD)	hr·ng/mL	175,800 (77,630)	163,000 (94,940)
$AUC_{0\text{-}24}$ (SD)	hr·ng/mL	86,500 (33,590)	95,210 (37,310)
C_{max} (SD)	ng/mL	6,512 (2,460)	7,154 (3,033)

$AUC_{0\text{-}24}$, area under the concentration-time curve from time 0 to the 24-hour time point; $AUC_{0\text{-}inf}$, area under the concentration-time curve from time 0 extrapolated to infinity; C_{max}, maximum observed plasma concentration; PK, pharmacokinetic.
*Data are presented as arithmetic mean with standard deviation.

Table 3. Statistical Comparison of Plasma Sparsentan PK Parameters Following Esomeprazole 40 mg + Sparsentan 800 mg Versus Sparsentan 800 mg Alone

Dependent	Unit	Esomeprazole + sparsentan*	Sparsentan alone*	GMR (%)†	CI 90 lower	CI 90 upper
$AUC_{0\text{-}inf}$	hr·ng/mL	161,500	146,100	110.58	101.37	120.63
$AUC_{0\text{-}t}$	hr·ng/mL	160,000	145,000	110.36	101.47	120.04
$AUC_{0\text{-}24}$	hr·ng/mL	81,000	89,100	90.59	83.03	98.84
C_{max}	ng/mL	6,137	6,696	91.66	81.66	102.87

ANOVA, analysis of variance; $AUC_{0\text{-}inf}$, area under the concentration-time curve from time 0 extrapolated to infinity; $AUC_{0\text{-}t}$, area under the concentration-time curve from time 0 to the last observed/non-zero concentration; $AUC_{0\text{-}24}$, area under the concentration-time curve from time 0 to the 24-hour time point; C_{max}, maximum observed plasma concentration; GeoLSM, geometric least-squares mean; GMR, geometric mean ratio; LSM, least-squares mean; PK, pharmacokinetic.
Parameters were ln-transformed prior to analysis.*Data are presented as GeoLSM; GeoLSMs were calculated by exponentiating the LSMs derived from the ANOVA. †GMR = 100×(test/reference).

CONCLUSIONS

- There was no significant difference in sparsentan's PK profile when administered alone compared to when coadministered with esomeprazole, indicating that changes in gastric pH did not affect sparsentan's exposure
- Based on this pH-dependent DDI study, sparsentan PK is not affected by the presence of ARAs, and dose adjustment would not be considered necessary when coadministered with ARAs

DISCLOSURES
KZD, DB, RK, MN, and **SK** are employees of Travere Therapeutics, Inc., and own stock or stock options in Travere Therapeutics, Inc.

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STATEMENT OF PURPOSE

- Immunoglobulin A nephropathy (IgAN) has a variable clinical presentation and heterogenous risk of progressive kidney function decline leading to kidney failure,[1,2] with approximately 20% to 30% of patients reaching kidney failure within 10 years and >50% doing so within 20 years[3,4]
- Sparsentan is a novel, nonimmunosuppressive, single-molecule, dual endothelin angiotensin receptor antagonist (DEARA) with high selectivity for the endothelin type A and angiotensin II type 1 receptors[5]
- In vitro solubility data indicated that sparsentan is a poorly soluble ampholyte with pH-dependent solubility lower at higher pH values[6]
- The current label indicates to avoid concomitant use of sparsentan with acid-reducing agents (ARAs) as it may decrease sparsentan's exposure[7]
- To assess the potential impact of gastric pH on sparsentan's pharmacokinetic (PK) profile, a physiologically based pharmacokinetic (PBPK) modeling pH sensitivity analysis investigated drug-drug interaction (DDI) between sparsentan and esomeprazole, an ARA, in a phase 1 study
- Esomeprazole increases gastric pH by inhibiting the H^+/K^+ ATPase enzyme (proton pump) and maintains intragastric pH >4.0 for most of the steady state.[8] Hence, esomeprazole can characterize the worst-case scenario of anticipated interaction due to its long-lasting effects on gastric pH[9]

DESCRIPTION OF METHODS AND MATERIALS

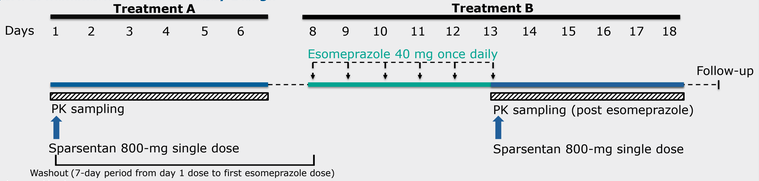
In vitro solubility study:
- Aqueous solubility of sparsentan was measured in various buffer and biorelevant media at 37°C. Aliquots (1.0 mL) of solution were taken at 1, 4, and 24 hours to determine sparsentan's concentration utilizing a suitable high-performance liquid chromatography method. pH of each solution was measured at the beginning (t=0) and end of work (24 hours)

The SimCyp in vitro data analysis (SIVA) toolkit:
- The SIVA toolkit (SimCyp v3, Certara, London, UK) was used to simulate and predict the in vivo absorption of sparsentan across different pH values that represent physiological pH conditions in the gastrointestinal tract. Physicochemical properties of sparsentan (molecular weight, Pka, logP, and intrinsic solubility), along with experimental data of in vitro solubility across a range of different pH values and formulation details, informed the model

PBPK pH sensitivity analysis:
- The bottom-up approach utilizing a default healthy volunteer population was employed to build a full-body PBPK model for sparsentan (SimCyp v19, Certara, London, UK).[10] In vitro data on pH-dependent solubility and permeability profiles of sparsentan, along with its physicochemical properties, informed the model. Additionally, in vitro data on CYP profiling were incorporated to account for metabolic clearance. The developed PBPK model for sparsentan was then employed to conduct a pH sensitivity analysis, predicting the impact of gastric pH on sparsentan's PK. Simulations were conducted by varying the physiological gastric pH value from 1.5 under fasted conditions to 5, which is expected after the administration of ARAs

Phase 1 clinical study:
Study design:
- A phase 1, 2-treatment, fixed-sequence study with an open-label design assessed the impact of ARAs on the PK profile of sparsentan in 20 healthy adult participants (**Figure 1**)

Figure 1. Schematic of Overall Study Design



PK, pharmacokinetics.

PK and statistical analysis of the data:
- The observed plasma concentrations of sparsentan were analyzed using noncompartmental analysis with Phoenix WinNonlin v8.4 (Certara, London, UK) to calculate sparsentan PK parameters
- An analysis of variance (ANOVA) model utilizing SAS v9.4 or higher evaluated esomeprazole's impact on sparsentan's PK. The ANOVA model computed the least-squares geometric mean (GeoLSM) values for maximum plasma concentration (C_{max}), area under the curve (AUC) up to 24 hours ($AUC_{0\text{-}24}$), and AUC to infinity ($AUC_{0\text{-}inf}$), alongside the ratio between treatment LSMs and the 90% CI of the ratio of LSMs. A drug interaction was considered present if the 90% CI of the ratio of LSMs between 2 treatments fell outside 80% to 125%

DISCUSSION

- Based on the findings from the in vitro solubility and SIVA analyses, it was anticipated that sparsentan's absorption would be reduced at higher pH levels
- The PBPK pH sensitivity analysis predicted lower absorption at higher pH values and an approximately 30% decrease in sparsentan's exposure after the gastric pH was increased to 5.0
- However, the clinical data showed that sparsentan's exposure was comparable when administered alone or in combination with esomeprazole
- We hypothesize that other factors might have played a role in maintaining the comparable sparsentan exposure at higher pH values, such as:
  - Changes in chemical degradation
  - Dissolution
  - Gut metabolism

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