Evaluation of Drug Interaction with Multiple Doses of Rabeprazole, a Proton Pump Inhibitor, on the Pharmacokinetics of Vadadustat

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National Kidney Foundation 2020 Spring Clinical Meetings – New Orleans, LA – March 25-29

BACKGROUND

- Vadadustat is a member of an emerging class of small molecules being developed as inhibitors of hypoxia-inducible factor prolyl-hydroxylases (HIF-PH), and is in the late stage of clinical development for the treatment of anemia due to chronic kidney disease (CKD).
- Vadadustat is orally bioavailable, rapidly absorbed (T_{max} ~2 hr), and eliminated by organs of excretion (liver and kidneys).
- In vitro dissolution studies have shown that the solubility of vadadustat increases with increasing pH (data not shown).
- Alteration of gastric acidity may alter the absorption of vadadustat.
- The rationale for this study was to evaluate the in vivo potential drug-drug interaction (DDI) of vadadustat pharmacokinetics (PK) in the presence of a gastric acid reducing agent, such as the proton pump inhibitor (PPI) rabeprazole.[1]

STUDY OBJECTIVES

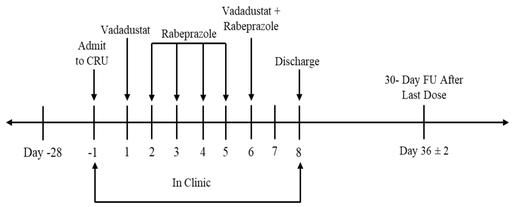
- The primary objective of this study was to assess the effect of oral rabeprazole 20 mg every 12 hours (Q12H) on the plasma PK profile of a single oral dose of vadadustat 300 mg.
- The secondary objective of this study was to assess the safety/tolerability of a single oral dose of vadadustat 300 mg co-administered with oral rabeprazole 20 mg Q12H, a dose demonstrated to be appropriate for evaluating the effects of increasing gastric pH in drug interaction studies.[2]

METHODS

Study Design

- This Phase 1, fixed-sequence, open-label study in healthy adult subjects was designed to evaluate the effect of multiple doses of rabeprazole on the PK of a single dose of vadadustat. (NCT03789032)
- The study consisted of a screening period (Days -28 to -2), a check-in (Day -1), a treatment period (Days 1 to 8), discharge of the subjects on Day 8, and a follow-up phone call 30 days (±2 days) post last dose. (Figure 1)

Figure 1. Study Design



CRU, Clinical Research Unit; FU, Follow-up

- Vadadustat Dose:
  - Participants received a single oral dose of 300 mg vadadustat on Day 1 and another dose in combination with oral rabeprazole (20 mg Q12H) on Day 6
  - A single dose of 300 mg vadadustat is appropriate for evaluation of the PK of vadadustat as it is within the therapeutic dose range and shown to be well tolerated in clinical studies.
  - A single dose was considered sufficient because the time-independent linear PK properties of vadadustat enable prediction of multiple-dose PK from single-dose PK profiles.

1 FDA. Guidance for Industry: Clinical Drug Interaction Studies – Study Design, Data Analysis and Clinical Implications. 2017.
2 Yago MR, Frymoyer A, Benet LZ, et al. The use of betaine HCl to enhance dasatinib absorption in healthy subjects with rabeprazole-induced hypochlorhydria. *AAPS J.* 2014;16(6):1358-65.

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- Participants (N=20):
  - The study population consisted of healthy male and female subjects at least 18 years of age and not more than 55 years of age. Eligible subjects were required to provide written informed consent.
  - Subjects were deemed healthy per Investigator judgment as documented by medical history, physical examination, vital sign assessments, 12-lead electrocardiograms (ECG), clinical laboratory assessments, and general observations.
  - Body mass index was between 18.0 and 30.0 kg/m^2, with a minimum body weight of 45 kg for females and 50 kg for males, inclusive.
  - Participants fasted until 4 hr post-vadadustat dosing.
- Assessments:
  - Blood samples were collected pre-dose and up to 48 hr post-dose for vadadustat PK evaluation on Day 1 and Day 6.
  - Primary endpoints were area under the plasma concentration-time curve from dosing to last quantifiable concentration ($AUC_{0\text{-}last}$) and to infinity ($AUC_{0\text{-}inf}$), as well as maximum plasma concentration (C_{max}); additional PK parameters included time to C_{max} (T_{max}) and elimination half-life ($t_{1/2}$).
  - Safety assessments included adverse events (AE), vital signs, clinical laboratory values, ECG, and physical examinations.

Table 1. Demographic Characteristics of Subjects Included in the PK Analysis Population

Characteristic	Category/Statistics	Overall, n (%)
No. of Subjects	**n**	**19**
Age	<18	0
	18-40	13 (68.4)
	>40	6 (31.6)
Gender	Male	7 (36.8)
	Female	12 (63.2)
Ethnicity	Hispanic or Latino	2 (10.5)
	Not Hispanic or Latino	17 (89.5)
Race	White	15 (78.9)
	Black	4 (21.1)
Characteristic	**Mean (SD)**	
Baseline Weight (kg)	74.30 (12.23)	
Height (cm)	168.42 (10.28)	

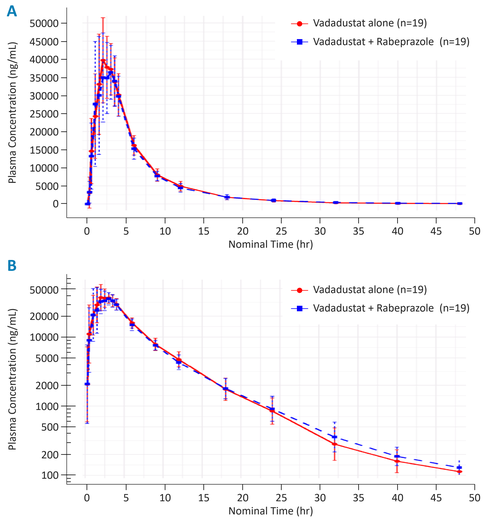
SD, standard deviation.

RESULTS

Disposition and Demographics

- The safety population enrollment was 20 subjects and the PK population included 19 subjects (1 subject was dosed and voluntarily withdrew from the study).
- Subjects ranged in age from 22 to 55 years old and the majority of subjects were white (80.0% in the safety population; 78.9% in the PK population) and female (60.0% in the safety population; 63.2% in the PK population).

Figure 2. Mean (ng/mL) Vadadustat Plasma Concentrations versus Time Profiles: (A) Linear scale (B) Semilogarithmic scale



Error bars = standard deviation.

PK Results (Table 2)

- When vadadustat was administered in combination with rabeprazole, there were no clinically relevant changes in the C_{max} and AUC values of vadadustat (Figure 2A and 2B).
- Mean AUC_{inf} was 254 hr*µg/mL for vadadustat alone and 245 hr*µg/mL for vadadustat plus rabeprazole. The $t_{½}$ was 5.23 and 6.01 hr for vadadustat alone and for vadadustat plus rabeprazole, respectively. The median T_{max} was 2.00 hr for vadadustat alone and 2.49 hr for vadadustat plus rabeprazole.
- Following treatment with vadadustat alone or vadadustat plus rabeprazole, point estimates of the Test/Reference mean ratios of the primary parameters AUC_{last}, AUC_{inf}, and C_{max} for vadadustat were 1.04, 1.04, and 1.03, respectively.

Safety Evaluation (Table 3)

- Treatment-emergent adverse events (TEAE) were reported by 5 (25%) subjects who received the first dose of vadadustat alone, 10 (50%) subjects who received rabeprazole alone, and 6 (32%) subjects who received both vadadustat and rabeprazole.
- The majority of TEAEs considered to be related to the study drug were reported in the rabeprazole-alone treatment arm.
- The most frequently reported TEAEs for vadadustat were: headache (35%), constipation (15%), abdominal pain (10%), and nausea (10%).
- Most of the AEs were mild in severity. There were no serious TEAEs or TEAEs leading to discontinuation or death.
- All abnormal clinical laboratory values and ECG recordings during the study were not clinically significant and no abnormal vital sign or physical examination measurements were recorded (data not shown).

Table 2. Summary of Plasma PK Parameters for Vadadustat. Geometric Mean (%CV)

PK Parameter (unit)	Vadadustat Alone (V)	Vadadustat + Rabeprazole (V + R)
AUC_{last} (hr*µg/mL)	252 (12.8)	243 (12.9)
AUC_{inf} (hr*µg/mL)	254 (12.9)	245 (12.8)
C_{max} (µg/mL)	47.1 (11.3)	45.8 (12.0)
$t_{1/2}$ (hr)	5.23 (15.0)	6.01 (14.1)
CL/F (mL/hr)	1.190 (12.5)	1.230 (11.9)
T_{max} (hr)*	2.00 (1.00 – 3.15)	2.49 (0.995 – 3.51)
GM Ratio $AUC_{0\text{-}last}$ **	N/A	1.04 (1.00 – 1.08)
GM Ratio $AUC_{0\text{-}inf}$ **	N/A	1.04 (0.99 – 1.07)
Gm Ratio C_{max} **	N/A	1.03 (0.99 – 1.07)

$AUC_{0\text{-}t}$: AUC from dosing (time 0) to infinity; AUC_{last}: AUC from dosing (time 0) to last quantifiable concentration; CL/F: apparent total body clearance; C_{max}: maximum observed plasma concentration; CV: coefficient of variation; GM: geometric mean; N: number of subjects included in the PK analysis population for each group; N/A: not applicable; $t_{½}$: elimination half-life; T_{max}: time of maximum plasma drug concentration.
* Presented as median (minimum – maximum)
** Vadadustat alone (Reference) was compared to vadadustat plus rabeprazole (Test) with respect to the AUC_{last}, AUC_{inf} and C_{max} for vadadustat, using an analysis of variance (ANOVA) with sequence, treatment, and period as fixed effects and subject (sequence) as a random effect after logarithmic transformation of the data. Point estimates and 90% confidence intervals (CI) for test/reference (T/R) of these parameters were calculated using this formula: Ratio= (R+V)/V *100. 90% Geometric CI (lower-upper)

Table 3. TEAEs

Overall Summary AEs n (%)		Vadadustat Alone (N=20)	Rabeprazole Alone (N=20)	Vadadustat + Rabeprazole (N=19)
Any TEAE		5 (25.0)	10 (50.0)	6 (31.6)
Severity	Mild	4 (20.0)	8 (40.0)	6 (31.6)
	Moderate	1 (5.0)	2 (10.0)	0
	Severe	0	0	0
Any Drug-Related TEAE		4 (20.0)	9 (45.0)	2 (10.5)
Any Drug-Related Serious TEAE		0	0	0
Any TEAEs Leading to Withdrawal From Treatment		0	0	0

N: number of subjects dosed; n (%): number and percent of subjects with at least one TEAE in each category. 'Drug-Related' refers to either of the two drugs.

CONCLUSIONS

- There were no clinically relevant changes in vadadustat PK exposure following co-administration of rabeprazole (Q12H 20 mg) and vadadustat (single dose, 300 mg).
- Since administration of vadadustat after treatment with rabeprazole did not affect exposure of vadadustat, it is unlikely that other acid-reducing agents (PPIs and H2 antagonists) will affect vadadustat exposure due to changes in gastric pH.
- Vadadustat and rabeprazole were generally well tolerated by subjects.

DISCLOSURES:

This study was funded by Akebia Therapeutics, Inc.

RS, SS, and AC: Employee and stockholder, Akebia Therapeutics, Inc., **SP:** Consultant, Akebia Therapeutics, Inc., **LB, BS:** Former employee and stockholder, Akebia Therapeutics, Inc.

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