Effect of Food Intake on the Pharmacokinetics of Vadadustat Following Single Dose Administration

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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 the liver and kidneys.
- Food intake is known to alter the pharmacokinetics (PK) of some orally administered drugs.[1]

STUDY OBJECTIVES

- The primary objective of these studies was to determine the effect of food on the PK of vadadustat during the stages of its clinical development.
- The secondary objective was to assess the safety/tolerability of a single oral dose of vadadustat 150 mg, 300 mg, and 450 mg under fasting and fed conditions.

METHODS

The effect of food on the PK of vadadustat was evaluated in multiple Phase 1 clinical studies of healthy adult subjects using different doses of vadadustat.

- **CI-0001**
  - Study CI-0001 was a single-ascending dose study to assess the safety, tolerability, PK, and pharmacodynamics (PD) of vadadustat in healthy subjects. The effect of food on the PK of vadadustat was also evaluated in this study.
  - A total of 5 subjects were administered a 300-mg capsule of vadadustat either under fasting conditions or were offered a standard meal under fed conditions.
  - Serial blood samples were collected at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hr post-dose.
- **CI-0013** (NCT02412449)
  - Study CI-0013 was an open-label, single-dose, randomized, crossover study conducted in healthy subjects to evaluate the effect of a high-fat meal on the bioavailability of a 150-mg film-coated tablet of vadadustat.
  - A total of 18 healthy subjects were enrolled. Subjects in the fasted group were fasted overnight for at least 10 hr prior to dosing and fasting conditions continued for 4 hr after dosing. Subjects in the fed group were fasted for at least 10 hr overnight prior to consuming a standardized FDA-defined, high-fat, high-calorie breakfast.[1] Subjects in the fed group consumed the high-fat breakfast beginning 30 min prior to dosing, and were required to consume the meal within 25 min.
  - Serial blood samples were collected at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hr post-dose.
- **CI-0028** (NCT03657290)
  - Study CI-0028 was an open-label, single-dose, randomized, crossover study conducted to compare the PK profile of vadadustat following the administration of a 450-mg film-coated tablet of vadadustat under fed and fasted conditions.
  - A total of 54 healthy subjects were enrolled. Subjects in the fasted group were fasted overnight for at least 10 hr prior to dosing; fasting conditions continued for 4 hr after dosing. Subjects in the fed group were fasted for at least 10 hr overnight prior to consuming a standardized FDA-defined, high-fat, high-calorie breakfast.[1] The meal started 30 min prior to dosing and was completed within 10 min before dosing.
  - Serial blood samples were collected at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 9, 12, 18, 24, 32, 40, and 48 hr post-dose.

[1]FDA. Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies. 2002.

SUMMARY OF THE CLINICAL STUDIES

- All studies were conducted in healthy subjects

Study	Dosing	Formulations	Dose (mg)	No. of subjects
CI-0001	Single dose of vadadustat	Capsule	300	5
CI-0013		Coated tablet	150	18
CI-0028		Coated tablet	450	54

RESULTS

PK RESULTS

- The vadadustat plasma concentration profiles for the PK analysis population in each study are presented in **Figures 1-3**.
- **CI-0001**
  - All 5 subjects (male: 100%, mean age: 31.6 years, body mass index [BMI]: 27 kg/m^2), successfully completed the course of 300-mg dosing of vadadustat and were included in the PK analysis.
  - The PK data for fed conditions showed that, in comparison with fasting conditions, there was a 15% decrease in maximum plasma concentration (C_{max}), a slight increase in time to maximal concentration (T_{max}), and a 5% increase in the area under the concentration-time curve (AUC), which was deemed not clinically relevant (**Table 1**).
- **CI-0013**
  - All 18 subjects (male: 66%, mean age: 31.9 years, BMI: 25 kg/m^2) completed the course of 150-mg dosing of vadadustat and were included in the PK analyses.
  - AUC values were approximately 20% lower and C_{max} was 28% lower in the presence of a high-fat breakfast compared to fasted conditions (**Table 1**).
  - The T_{max} values were 2.0 and 1.5 hr, respectively, when vadadustat was administered in fed conditions compared to fasted conditions, although the range of values was identical between the 2 treatments (1.0 to 5.0 hr) (**Table 1**).
- **CI-0028**
  - Of the 54 healthy subjects (male: 48%, mean age: 36 years, BMI: 26 kg/m^2) enrolled, 2 subjects withdrew at their own request, and 52 subjects were included in the PK analysis population.
  - AUC values were about 6% lower and the C_{max} value was about 25% lower when vadadustat was given under fed conditions compared to when it was administered under fasted conditions. The T_{max} value significantly increased in the presence of a high-fat meal from 2.0 to 3.5 hr (**Table 1**).

SAFETY RESULTS

- **CI-0001**
  - In the fed cohort, 1 subject (20%) experienced an adverse event (AE), which the investigator considered to be unrelated to the study drug.
  - There were no serious or significant AEs.
  - There were no clinically significant abnormalities, including laboratory results, that were considered a serious AE or resulted in discontinuation from the study.
- **CI-0013**
  - In both the fasted and fed groups, 2 subjects (11.1%) experienced AEs.
  - The investigators assessed the reported AEs as possibly related to the study drug. The AEs were mild in severity and self-limiting. No action was taken to treat any of the reported AEs.
  - There were no discontinuations from the study due to AEs.
- **CI-0028**
  - Among participants studied under fasted conditions, 17 subjects (31.5%) experienced AEs after receiving vadadustat. Of those studied under fed conditions, 7 subjects (13.2%) experienced AEs.
  - The investigator considered all AEs to be mild or moderate in severity. One treatment-emergent adverse event (TEAE), leading to treatment withdrawal was reported. However, the event was classified as moderate, but not related to the study drug.

Table 1. Summary of Plasma PK Parameters for Vadadustat

PK parameter Geometric mean (%CV)	CI-0001 (300-mg capsule) n=5		CI-0013 (150-mg coated tablet) n=18		CI-0028 (450-mg coated tablet) n=52*	
	Fasted	Fed	Fasted	Fed	Fasted	Fed
AUC_{last} (hr*µg/mL)	183.3 (17)	192.2 (20)	106.0 (25)	85.0 (22)	357 (27)	337 (28)
AUC_{inf} (hr*µg/mL)	188.3 (17)	197.9 (20)	109.6 (27)	87.5 (23)	359 (27)	339 (28)
C_{max} (µg/mL)	30.9 (7)	26.3 (27)	20.6 (24)	14.8 (17)	61.5 (25)	44.9 (26)
T_{max} (hr)**	3.0 (1.5 – 4.1)	3.0 (1.5 – 6.0)	1.5 (1.0 – 5.0)	2.0 (1.0 – 5.0)	2.0 (0.97 – 6.0)	3.5 (1.0 – 8.97)
GM Ratio (90% CI)* **						
GM Ratio % C_{max}	N/A	85.1 (67.8 – 106.9)	N/A	72.0 (64.9 – 79.9)	N/A	73.1 (67.9 – 78.6)
GM Ratio % $AUC_{0\text{-}inf}$	N/A	105.1 (84.6 – 130.6)	N/A	79.8 (74.3 – 85.6)	N/A	94.3 (90.3 – 98.5)

AUC_{inf}: AUC from dosing (time 0) to infinity; AUC_{last}: AUC from dosing (time 0) to last quantifiable concentration; CI: confidence interval; 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_{max}: time of maximum plasma drug concentration.
* Two subjects withdrew from the study, resulting in 52 subjects for PK analysis.
** Presented as median (minimum – maximum)
*** GM ratio: % ratio (fed/fasted). Two treatments are said to be (average) bioequivalence if the 90% CI of the ratio of GM of the test (fed) and reference (fasted) treatment for the primary PK parameters was within the bioequivalence limits of 80.00% and 125.00%.

Figure 1. Study CI-0001 (300 mg) – Arithmetic Mean (µg/mL) Vadadustat Plasma Concentrations versus Time Profiles on linear scale (inset: semilogarithmic scale)

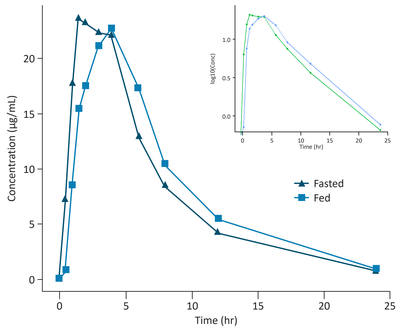


Figure 2. Study CI-0013 (150 mg) – Arithmetic Mean (µg/mL) Vadadustat Plasma Concentrations versus Time Profiles on linear scale (inset: semilogarithmic scale)

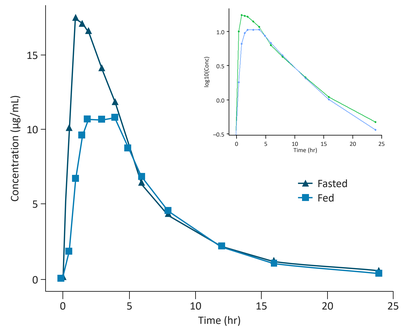
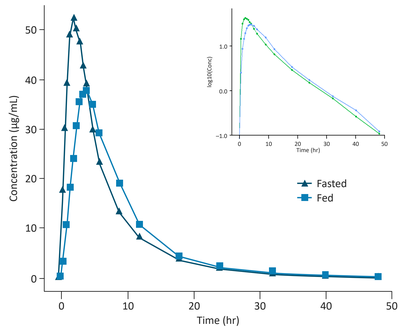


Figure 3. Study CI-0028 (450 mg) – Arithmetic Mean (µg/mL) Vadadustat Plasma Concentrations versus Time Profiles on linear scale (inset: semilogarithmic scale)



CONCLUSIONS

- Across all three studies, vadadustat absorption was slightly delayed in the presence of food.
- Exposures to vadadustat (AUC) were similar in the presence of food compared to fasted conditions at both the 300 mg and 450 mg dose levels, and were slightly lower at the 150 mg dose. These changes in exposures were not considered clinically relevant.
- Vadadustat may be taken without regard to food intake.
- Vadadustat was generally well tolerated by healthy subjects under fasted and fed conditions.

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RS, PNG, 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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