Effect of Moderate Hepatic Impairment on Pharmacokinetics of Vadadustat, an Oral Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor (HIF-PHI)

Ajit Chavan, PhD; Susan Paulson, PhD; Leontia Burke, MS; Rishikesh Sawant, PhD; Brian Schwartz MD; Emil deGoma, MD

Akebia Therapeutics, Inc., Cambridge, MA, USA

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BACKGROUND

- Vadadustat is a member of an emerging class of drugs which inhibit hypoxia-inducible factor prolyl-hydroxylases (HIF-PHI). Vadadustat is being developed for the treatment of anemia due to chronic kidney disease (CKD).
- Vadadustat is orally bioavailable, rapidly absorbed, and eliminated by organs of excretion (liver and kidney).
- Vadadustat is primarily metabolized to O-glucuronide by UPD-glucuronosyltransferases (UGTs). The predominant UGT involved in the metabolism of vadadustat is UGT1A9 with minor contributions from UGT1A1 and extra-hepatic UGT1A7/1A8. UGT1A9 is expressed in the liver and kidney.
- There is potential that the pharmacokinetics of vadadustat may be altered in subjects with hepatic impairment. However, in general, metabolism by glucuronidation is shown not to be impacted by liver insufficiency.[1]
- Therefore, the role of hepatic impairment in vadadustat clearance was evaluated.[2]

METHODS

- Study Design: This phase 1, open-label, parallel-group, single-dose study evaluated the PK and safety following 450 mg vadadustat administration (NCT03799848, **Figure 1**).
- Vadadustat Dose:
  - Participants received a single oral dose of 450 mg vadadustat on Day 1.
  - A single dose of 450 mg vadadustat is appropriate for evaluation of vadadustat PK 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 enables prediction of multiple-dose PK from single-dose PK profiles.
- Participants (N=8 hepatic impairment; N=8 normal):
  - Participants were adults between 18 and 70 years of age, inclusive, with either normal hepatic function or moderate hepatic impairment (Child-Pugh Class B).
  - Typical exclusion criteria were applied, including history of alcohol or drug abuse, clinically significant abnormal laboratory findings, recent surgery, and select concomitant medications such as any erythropoiesis-stimulating agents within 30 days prior to dosing.
  - Participants with normal hepatic function were matched by gender, race, age (± 5 years), weight (± 15%), and BMI (± 15%), to participants with moderate hepatic impairment.
  - Participants fasted at least 10 hours prior to dosing and until 4 hours post vadadustat dosing.
  - Subjects with renal impairment (≥ Stage 3; eGFR < 60 mL/min) were excluded from this study.
- PK and Safety Assessments:
  - Blood samples were collected pre-dose and up to 72 hours post-dose for PK evaluation.
  - 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 (AEs), vital signs, clinical laboratory values, electrocardiograms (ECG), and physical examinations.

[1] Hoyumpa AM and S. Schenker. "Is glucuronidation truly preserved in patients with liver diseases?" (1991), **Hepatology** 13: 786-795.
[2] FDA . Guidance for Industry: Pharmacokinetics inpatients with impaired hepatic function: study design, data analysis, and impact on dosing and labeling. 2003.

RESULTS

Figure 1. Study Design

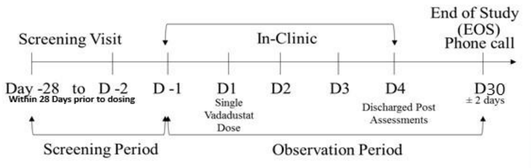


Table 1. Subject Demographics

Characteristic	Moderate Hepatic Impairment (n=8)	Normal Hepatic Function (n=8)	Overall (N=16)
Age, mean (SD), y	59.5 (5.4)	58.9 (7.2)	59.2 (6.1)
Gender, n (%)			
Male	3 (37.5)	3 (37.5)	6 (37.5)
Female	5 (62.5)	5 (62.5)	10 (62.5)
Weight, mean (SD), kg	80.6 (10.0)	83.6 (9.1)	82.1 (9.4)
BMI, mean (SD), kg/m²	28.8 (3.1)	29.9 (3.0)	29.4 (3.0)
White, n (%)	8 (100.0)	8 (100.0)	16 (100.0)
Ethnicity, n (%)			
Hispanic or Latino	4 (50.0)	5 (62.5)	9 (56.3)
Not Hispanic or Latino	4 (50.0)	3 (37.5)	7 (43.8)

BMI, body mass index; SD, standard deviation.

Table 2. Individual Child-Pugh's Classification Score and Laboratory Values for Moderate Hepatic Impairment Subjects

Patient No.	Laboratory Values at Baseline			Total CP Score
	Albumin (g/dL)**	Bilirubin (mg/dL)	PT (sec)	
1-105	4	2.9	16	7
1-107	3.6	1.3	16.3	7
1-114	4.1	2.7	13.2	8
3-101	4.2	0.7	11.3	7
3-102	3.7	4.3	14.3	9
3-103	3.8	1.1	11.7	7
3-104	4.2	1.5	11.5	7
3-105	3.8	1.9	12.6	7

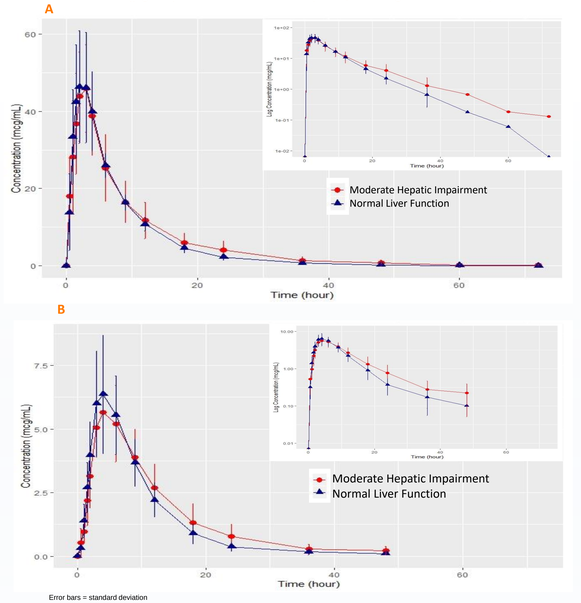
*Abbreviation: CP, Child-Pugh; PT, Prothrombin time
** Values reported were at the time of screening
CP categories are classified based on score, if 5 or 6 (CP-A, mild), if 7-9 (CP-B, moderate), if 10 to 15 (CP-C, severe).[2]

Results

Disposition and Demographics

- Sixteen participants were enrolled, 8 with normal hepatic function and 8 with moderate hepatic impairment; all completed the study and were included in both the safety and pharmacokinetic analysis populations.
- Demographic characteristics were similar between the hepatic function groups; all participants were white with a mean age of 59.2 years; most (62.5%) were female (**Table 1**).
- The laboratory values associated with Child-Pugh classification and scores are presented in **Table 2**.

Figure 2. Arithmetic Mean Plasma Vadadustat (A) and O-glucuronide (B) Concentrations (µg/mL) versus Time Profiles (inset, semilogarithmic scale)



Error bars = standard deviation

Pharmacokinetic Results

- After a single 450 mg dose of vadadustat, plasma exposure (AUC) was slightly higher in participants with moderate hepatic impairment compared with those with normal hepatic function; C_{max} was similar between groups (**Figure 2, Table 3**).
- Point estimates of the hepatic impairment/normal function geometric mean ratios for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} were 1.05, 1.06, and 1.02, respectively (**Table 3**).
- Median T_{max} was 2 hours and 2.5 hours in the moderate and normal hepatic function groups, respectively. Mean elimination half-life was 7.75 hours in the hepatic impairment group compared to 5.81 hours in the normal hepatic function group (**Table 3**).

Safety

- Safety profiles were similar following a single dose of 450 mg vadadustat between participants with normal hepatic function and those with moderate hepatic impairment.
- In the moderate hepatic impairment group, a total of 3 TEAEs were reported by 1 participant (1 related event of constipation and 2 unrelated events of ecchymosis; **Table 4**).
- In the normal hepatic function group, a total of 4 TEAEs were reported by 2 participants (1 related event and 1 unrelated event of nausea, 1 related event of fatigue, and 1 related event of headache; **Table 4**).
- Most TEAEs (86%) were mild in severity; none were severe, and all resolved by the end of study.
- There were no serious TEAEs or TEAEs leading to discontinuation or death.
- There were no clinically significant findings reported for laboratory tests, vital signs, or ECGs.

Table 3. Summary of Plasma PK Parameters for Vadadustat and O-glucuronide (Mean ± SD)

PK Parameters	Vadadustat Parent		Vadadustat O-glucuronide	
	Moderate Hepatic Impairment (n=8)	Normal Liver Function (n=8)	Moderate Hepatic Impairment (n=8)	Normal Liver Function (n=8)
$AUC_{0\text{-last}}$ (µg*hr/mL)	432±153	395±72	68.9±24.2	62.5±21.3
$AUC_{0\text{-inf}}$ (µg*hr/mL)	436±156	397±72	70.9±24.3	63.8±21.3
C_{max} (µg/mL)	53±12	53±15	5.85±1.5	6.65±2.4
T_{max}** (hr)	2.0 (1.0, 4.0)	2.5 (1.5, 6.0)	NA	NA
Clearance (CL/F; L/hr)	1.2±0.4	1.2±0.3	NA	NA
Volume of distribution (Vd/F; L)	12.3±4.0	9.6±1.9	NA	NA
Elimination Half-life ($T_{1/2}$; hr)	7.75±2.5	5.81±1.4	6.01±2.1	4.74±1.3
GM Ratio $AUC_{0\text{-last}}$	1.05 (0.82-1.35)	NA	NC	NA
GM Ratio $AUC_{0\text{-inf}}$	1.06 (0.82-1.36)	NA	NC	NA
GM Ratio C_{max}	1.02 (0.79-1.32)	NA	NC	NA

*Abbreviation: $AUC_{0\text{-inf}}$: AUC from dosing (time 0) to infinity; $AUC_{0\text{-last}}$: AUC from dosing (time 0) to last quantifiable concentration; Cmax: maximum observed plasma concentration; N: number of subjects included in the PK analysis population for each group; NA: not applicable; NC: not calculated: SD: standard deviation;
** Presented as median (minimum, maximum)

Table 4. Treatment Emergent Adverse Events (TEAEs)

MedDRA System Preferred Term	Moderate Hepatic Impairment (n=8)		Normal Hepatic Function (n=8)		Overall (n=16)	
	n (%)	No. of Events	n (%)	No. of Events	n (%)	No. of Events
Any TEAE	1 (12.5)	3	2 (25.0)	4	3 (18.8)	7
Any Serious TEAE	0	0	0	0	0	0
Any TEAE Leading to Discontinuation	0	0	0	0	0	0
Death	0	0	0	0	0	0
TEAE						
Nausea	0	0	2 (25.0)	2	2 (12.5)	2
Constipation	1 (12.5)	1	0	0	1 (6.3)	1
Ecchymosis	1 (12.5)	2	0	0	1 (6.3)	2
Fatigue	0	0	1 (12.5)	1	1 (6.3)	1
Headache	0	0	1 (12.5)	1	1 (6.3)	1

MedDRA = Medical Dictionary for Regulatory Activities

CONCLUSIONS

- Moderate hepatic impairment did not alter peak vadadustat plasma levels, nor had meaningful impact on vadadustat total systemic exposure.
- In this single dose study at 450 mg, vadadustat was well tolerated with a similar incidence of TEAEs in those with either normal or moderately impaired hepatic function.

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AC: Akebia Therapeutics, Inc. (Akebia) **SP:** Consultant, Paulson PK Consulting LLC., **LB:** Formerly with Akebia, **RS:** Akebia, **BS:** Formerly with Akebia, **EdG:** Formerly with Akebia
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