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

**BACKGROUND**

- Vadadustat is a member of an emerging class of drugs that inhibit hypoxia-inducible factor prolyl hydroxylase (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 Gluconolactone by UGT glucuronidase/transferrases (UGT). The elimination rate of vadadustat is UGT1A9 with minor contributions from UGT1A1 and extra hepatic UGT1A6/UGT1A1 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.
- Therefore, the role of hepatic impairment in vadadustat clearance was evaluated.

**METHODS**

**Study Design:** This Phase I, open-label, parallel-group, single-dose study evaluated the PK and safety following a single 450 mg vadadustat administration (NCT03701486; Figure 1).

**Vadadustat Dosing:**
- 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 therapeutically relevant 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 predictions of multiple-dose PK from single-dose PK profiles.
- Participants (HFI, hepatic impairment, HFI-normal).
- Participants were adults aged 18 years and older, 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 an erythropoiesis-stimulating agent) within 30 days prior to dosing.
- Participants with normal hepatic function were matched by gender, race, age (±5 years), weight (±10%, and BMI (±10%), to participants with moderate hepatic impairment.
- Participants fasted at least 3 hours prior to dosing and until 4 hours post-dosing vadadustat.
- Subjects with renal impairment (Stage 5, GFR < 20 ml/min/1.73 m²) 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.
- A single dose was given under the plasma concentration time course from dosing to last quantifiable concentration (Cmax) and to infinity (Cmax). As well as maximum plasma concentration (Cmax,0-28h). Additional PK parameters included time to Cmax (tmax,0-28h) and elimination half-life (t1/2).
- Safety assessments included adverse events (AEs), vital signs, clinical laboratory values, electrocardiograms (ECGs), and physical examination.

**RESULTS**

**PK Parameters**

- Dose of 450 mg vadadustat was administered to participants with normal (n=8) and moderate hepatic impairment (n=8).
- Pharmacokinetic parameters for vadadustat were determined at screening (Day 1) and on the final day of dosing (Day 28).
- For vadadustat, both the mean peak plasma concentration (Cmax) and area under the plasma concentration-time curve over the dosing interval (AUC) were similar between the two groups (Figure 2, Table 3).
- There was a 4.74-fold increase in Cmax and a 4.02-fold increase in AUC in the moderate hepatic impairment group compared to the normal liver 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 5 participants (1 related event of constipation and 2 unrelated events of hyperventilation; 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 constipation, 1 unrelated event of fatigue, and 1 related event of headache; Table 4).

- Most TEAEs (91%) were mild in severity; none were severe, and all resolved by the end of the 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.

**DISCUSSIONS AND FUNDING:**

- Moderate hepatic impairment did not alter peak vadadustat plasma levels, nor had it meaningful impact on vadadustat 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.

**REFERENCES:**


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