A Drug-Drug Interaction Study to Evaluate the Effect of Vadadustat on the Pharmacokinetics of Celecoxib—a CYP2C9 Substrate—in Healthy Volunteers

Gurudatt A. Chandorkar\(^1\), Ramin Farzaneh-Far\(^2\), Akshay Buch\(^1\), and Bradley Maroni\(^2\)
\(^1\)Clinical Pharmacology, Akebia Therapeutics, Inc., Cambridge, MA, USA; \(^2\)Medical Research, Akebia Therapeutics, Inc., Cambridge, MA, USA

Abstract

Introduction and Aims: Vadadustat is a novel, orally-administered, small molecule activator of hypoxia-inducible factor (HIF) in development for the treatment of anemia associated with chronic kidney disease. In vitro studies suggest vadadustat is a weak inhibitor of the cytochrome P450 (CYP) isoenzyme, CYP2C9. Since CYP2C9 is involved in the metabolism of many commonly prescribed drugs (eg, rosuvastatin and losartan), the objective of this study was to determine whether vadadustat acts as a CYP2C9 inhibitor in vivo, using celecoxib as a sensitive CYP2C9 substrate.

Methods: This was an open-label, single-sequence, drug interaction study in healthy male patients (N=12). All patients received a single oral dose of celecoxib (200 mg) on Day 1. Oral doses of vadadustat (600 mg) were then administered on Days 3–9 inclusive. Celecoxib was co-administered with vadadustat on Day 8. Serial blood samples were collected over a 48-hour period to determine the concentrations of celecoxib when administered alone (Day 1) and when co-administered with vadadustat (Day 8). Plasma samples for celecoxib were analyzed using validated LC/MS/MS methods. Drug-drug interaction (DDI) was assessed by evaluating the geometric mean ratios for AUC\(_{0-t}\) and AUC\(_{0-inf}\), no significant differences were found between C\(_{max}\), AUC\(_{max}\), and AUC\(_{area}\) for celecoxib when dosed with vadadustat (test) compared to celecoxib administered alone (reference). The safety and tolerability of the single dose of celecoxib alone and in combination with multiple daily doses of vadadustat were assessed by collection of vital signs, clinical laboratory parameters, and adverse event (AE) reporting.

Results: The mean half-life (t\(_{1/2}\)) of celecoxib was similar in the presence (10.5 h) and absence (10.8 h) of vadadustat. Co-administration of vadadustat and celecoxib resulted in a 12% and 11% increase in celecoxib AUC\(_{0-t}\) and AUC\(_{0-inf}\), respectively, and a 60% increase in C\(_{max}\). Based on the 90% confidence intervals for the geometric mean ratios (Test/Reference) and the 90% confidence intervals of plasma C\(_{max}\), AUC\(_{max}\), and AUC\(_{area}\) for celecoxib when dosed with vadadustat (test) compared to celecoxib administered alone (reference). The safety and tolerability of the single dose of celecoxib alone and in combination with multiple daily doses of vadadustat were assessed by collection of vital signs, clinical laboratory parameters, and adverse event (AE) reporting.

Conclusions: The similarity in celecoxib AUC when dosed with or without vadadustat, indicates that vadadustat has no clinically significant interaction with CYP2C9-sensitive substrates. The transient effect on celecoxib C\(_{max}\) is not considered clinically relevant. Vadadustat may be administered with medications metabolized by CYP2C9 without the need to modify the dose of the co-administered drug.

Background

Vadadustat

• Vadadustat is a small molecule inhibitor of HIF prolyl-hydroxylases (HF-PH)
• HF is the primary regulator of the production of red blood cells (RBCs) and acts by modulating the body’s physiologic response to hypoxia
• By inhibiting HF-PH enzymes, vadadustat stabilizes HF proteins resulting in an increase in erythropoietin (EPO) secretion, RBC production, and iron delivery to the bone marrow

Clinical Development of Vadadustat

• Being developed for the treatment of anemia secondary to chronic kidney disease (CKD)
• To date, it has beenevaluated in 15 completed Phase 1 and Phase 2 studies and is well-tolerated in both healthy volunteers and CKD patients
• Administered as once-daily oral tablets and dose adjusted based on a patient’s hemoglobin response
• Induces diurnal variation in EPO concentrations while maintaining physiologic range
• Facilitates iron homoeostasis by decreasing levels of hepcidin and ferritin, as well as increasing total iron binding capacity

Pharmacokinetics of Vadadustat

• Vadadustat is an orally bioavailable molecule with a half-life of approximately 4 hours in healthy volunteers allowing once-a-day dosing
• Vadadustat is metabolized to pharmacologically inactive O- and N-glucuronides and undergoes dual clearance via urinary excretion and fecal elimination
• In vitro data suggests that vadadustat does not inhibit CYP3A4 and, therefore, interactions with drugs such as etoricoxib are highly unlikely
• Based on in vitro data, vadadustat is a weak inhibitor of CYP2C9
• Here we present the results from a study in healthy volunteers receiving vadadustat and the CYP2C9 substrate celecoxib

Study Design

Methods:

• Celecoxib was chosen for this study as a known CYP2C9 sensitive substrate for use in FDA guidelines on drug interaction studies

• Open-label, sequential, drug-interaction study

• All patients received a single oral dose of 200 mg celecoxib on Day 1

• Oral doses of 600 mg vadadustat (four 150 mg tablets) were administered on Days 3–9 inclusive

• Celecoxib was co-administered with vadadustat on Day 8

• Serial blood samples were collected over a 48-hour period to determine the concentrations of celecoxib when administered alone (Day 1) and when co-administered with vadadustat (Day 8) in a fasted state

• Plasma samples for celecoxib were analyzed using validated LC/MS/MS methods

Inclusion Criteria

• Healthy male patients age 18–55 years old with a body mass index of 18–30 kg/m\(^2\) who are homogeneous for the extensive metabolizer, CYP2C9*2 allele

Endpoints

• Plasma PK parameters following a single 200 mg dose of celecoxib administered alone on Day 1 and when co-administered with vadadustat on Day 8
• Safety and tolerability of seven consecutive daily doses of vadadustat 600 mg
• Safety and tolerability of celecoxib administered alone and following multiple daily doses of vadadustat

Demographics, Baseline Characteristics, and Patient Disposition

Conclusions

• Vadadustat may be administered with medications metabolized by CYP2C9 without the need to modify the dose of the co-administered drug
• The increase in C\(_{max}\) of celecoxib administered with vadadustat versus alone appeared to be transient since the impact on the overall extent of absorption (AUC) was minimal, and other PK parameters (t\(_{max}\) and CL/F) were unaffected
• Vadadustat was well-tolerated when administered concomitantly with celecoxib

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