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

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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 that 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 (Test/Reference) and the 90% confidence intervals of plasma C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ for celecoxib when dosed with vadadustat (test) compared to celecoxib administered alone (reference). The safety and tolerability of the single doses of celecoxib alone and in combination with multiple daily dosing of vadadustat were assessed by collection of vital signs, clinical laboratory parameters, and adverse event (AE) reporting.

Results: The mean half-life ($t_{½}$) of celecoxib was similar in the presence (10.3 hr) and absence (10.8 hr) of vadadustat. Co-administration of vadadustat and celecoxib resulted in a 12% and 11% increase in celecoxib $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$, respectively, and a 60% increase in C_{max}. Based on the 90% confidence intervals for the geometric mean ratios for $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$, no significant DDI was observed between vadadustat and celecoxib. Two mild AEs (flushing and headache) were reported in 2 patients.

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 (HIF-PH)
- HIF is the primary regulator of the production of red blood cells (RBCs) and acts by simulating the body's physiologic response to hypoxia
- By inhibiting HIF-PH enzymes, vadadustat stabilizes HIF 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 been evaluated 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 homeostasis by decreasing levels of hepcidin and ferritin, as well as increasing total iron binding capacity

Pharmacokinetics of Vadadustat

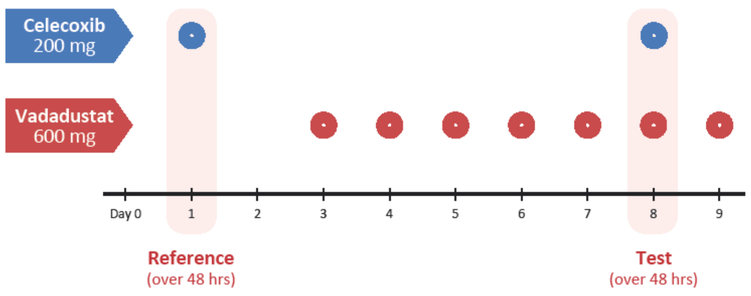
- Vadadustat is an orally bioavailable molecule with a half-life of approximately 4 hours in healthy volunteers allowing once-a-day dosing
- Vadadustat is metabolized to pharmacologically inactive O- and acyl-glucuronides and undergoes dual clearance via urinary excretion and fecal elimination
- *In vitro* data suggests that vadadustat does not inhibit CYP3A4 and, therefore, interactions with drugs such as atorvastatin 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 per US FDA guidelines on drug interaction studies

Dosing Shedule



- 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 homozygous for the extensive metabolizer *CYP2C9*1* 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

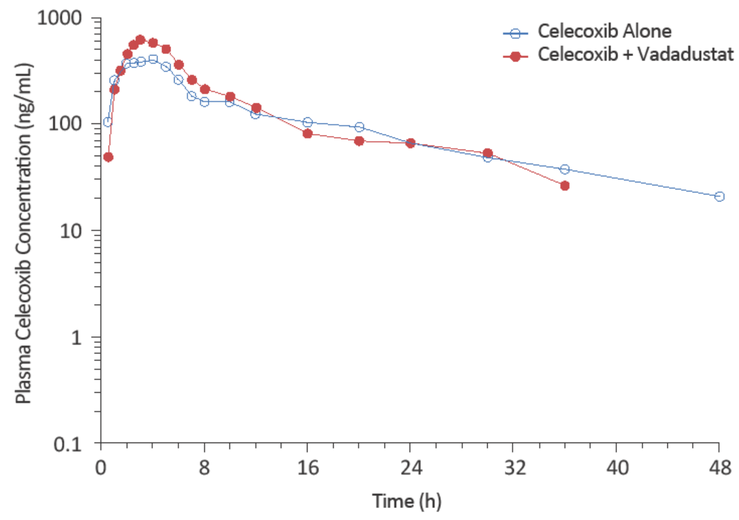
Demographics, Baseline Characteristics, and Patient Disposition

Parameter	Total (N=12)
Gender (male) [a]	12 (100%)
Age (years) [b]	36.8 (23–54)
Race [a]	
White/Caucasian	6 (50.0%)
Black or African American	4 (33.3%)
Other	2 (16.7%)
Height (cm) [c]	178 ± 8.35
Weight (kg) [c]	81.4 ± 12.5
Body Mass Index (kg/m^2) [c]	25.6 ± 2.11
Patients who completed study participation [a]	12 (100%)

a Number of patients (%)
b Mean value (min–max)
c Mean value ± standard deviation

Results

Plasma Celecoxib Concentration-Time Profiles



Plasma Celecoxib Pharmacokinetic Parameters

PK Parameter [a]	Celecoxib Alone: Day 1 (N=12)	Celecoxib + Vadadustat: Day 8 (N=12)
$AUC_{0\text{-}t}$ (h*ng/mL) [b]	4804 ± 1029	5472 ± 1549
$AUC_{0\text{-}inf}$ (h*ng/mL) [c]	5160 ± 1109	5755 ± 1480
C_{max} (ng/mL) [d]	517 ± 190	800 ± 261
T_{max} (hours) [e]	3.00 (1.00 – 5.00)	2.75 (1.50 – 5.00)
$t_{½}$ (hours) [f]	10.8 ± 5.24	10.3 ± 5.67
CL/F (L/h) [g]	40.7 ± 10.0	37.2 ± 10.9

a Mean value ± standard deviation; T_{max} presented as Median value (min–max)
b $AUC_{0\text{-}t}$: Area under the concentration-time curve calculated from time zero to the time of the last quantifiable concentration
c $AUC_{0\text{-}inf}$: Area under the concentration-time curve from time zero to infinity
d C_{max}: maximum plasma drug concentration
e T_{max}: time of maximum plasma drug concentration
f $t_{½}$: terminal half-life
g CL/F: oral clearance

- Celecoxib AUC was similar when dosed with or without vadadustat (12% and 11% increase, respectfully). A 60% increase in C_{max} was observed
- The mean half-life of celecoxib was similar in the presence (10.3 hr) and absence (10.8 hr) of vadadustat

Geometric Means Ratios for the PK Parameters of Celecoxib Administered Alone and with Vadadustat

PK Parameter	Geometric Mean Ratio [a]	90% Confidence Interval
$AUC_{0\text{-}t}$ (h*ng/mL)	1.12	1.03 – 1.22
$AUC_{0\text{-}inf}$ (h*ng/mL)	1.11	1.03 – 1.20
C_{max} (ng/mL)	1.60	1.35 – 1.91

a Geometric mean ratio = (celecoxib + vadadustat) / celecoxib alone

- No significant drug-drug interaction was observed between vadadustat and celecoxib based on the 90% confidence intervals for the geometric mean ratios for $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$

Summary of Adverse Events

	Sequential Treatments (N=12)		
	Celecoxib Alone (Day 1)	Vadadustat Alone (Days 3 - 7)	Celecoxib + Vadadustat (Day 8)
Number of patients with AEs	0	2	0
Number of AEs	0	2	0
Number of drug-related AEs	0	1	0
Number of patients withdrawn due to AEs	0	0	0

- Two adverse events of mild headache and mild flushing were reported in 2 patients
- Both events resolved without requiring treatment and did not recur with continued dosing of vadadustat

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 ($t_{½}$ and CL/F) were unaffected
- Vadadustat was well-tolerated when administered concomitantly with celecoxib

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