Vadadustat Does Not Prolong Corrected QT Interval in a Thorough QTc Study in Healthy Subjects

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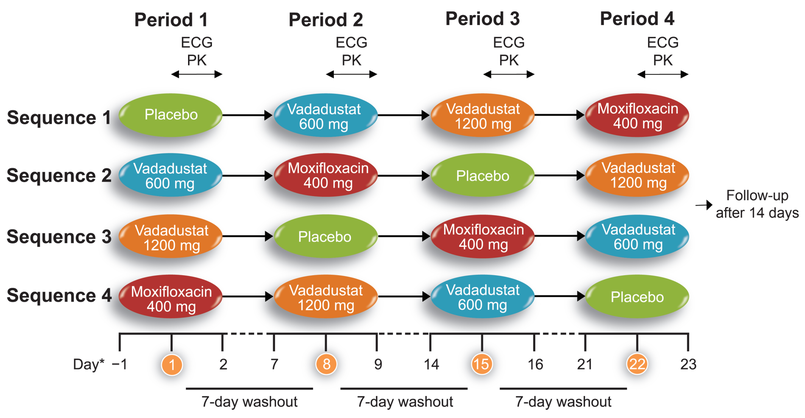
Introduction

- Vadadustat is a hypoxia-inducible factor prolyl-hydroxylase domain inhibitor that is currently in development for the treatment of anemia associated with chronic kidney disease (CKD).
- Regulatory guidance ICH E14 recommends assessing the proarrhythmic potential of new clinical entities by thorough electrocardiographic (ECG) assessment of QTc (QT interval corrected for heart rate).[1]
- Patients with CKD are at high risk of arrhythmic cardiovascular events, frequently exhibit cardiac repolarization abnormalities, and are exposed to electrolyte shifts.[2,3] QTc prolongation—a finding on 12-lead ECG, indicative of delayed cardiac repolarization—is highly prevalent among patients with CKD,[3-6] affecting up to 65% of patients with end-stage renal disease,[6] and is associated with an increased risk of cardiovascular death.[7]
- Preclinical studies (in vitro hERG potassium channel assay and in vivo studies in dogs) did not raise any concern for QTc prolongation with vadadustat.[8]
- The effect of vadadustat on cardiac repolarization was assessed in a thorough QT (TQT) study in healthy human subjects (NCT02062203).

Methods

- This was a standard TQT, randomized crossover study; it comprised 4 sequential periods where a single dose of the following was administered: therapeutic study drug (vadadustat 600 mg) supratherapeutic study drug (vadadustat 1200 mg), placebo, and active control (moxifloxacin 400 mg) (**Figure 1; Table 1**).

Figure 1. Study design



*Subjects were admitted to a clinical research unit on days −1, 7, 14, and 21; and discharged on days 2, 9, 16, and 23, respectively. Dosing days were 1, 8, 15, and 22. Subjects received a single oral dose of vadadustat (600 mg or 1200 mg) or placebo (all blinded), or moxifloxacin 400 mg (open-label) under fasting conditions. ECG, continuous electrocardiography from −1 to 25 hours; PK, pharmacokinetic sampling from 0–24 hours.

Table 1. Key inclusion and exclusion criteria

Inclusion	• Healthy nonsmoking male and female adults (age 18–55 years) • Body mass index of 18.0–32.0 kg/m^2
Exclusion	• Significant cardiovascular, pulmonary, or other disease • Unexplained syncope, cardiac arrest, unexplained cardiac arrhythmias, structural heart disease, or family history of Long QT syndrome

- The study was double-blinded for the vadadustat and placebo treatments and open-label for the moxifloxacin treatment (**Figure 1**).
- During each treatment period, 12-lead ECGs (10 replicates) were obtained at baseline (predose) and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose.
- Central, blinded manual adjudication of automated interval measurements was performed, and QT was corrected for heart rate using Fridericia's formula (QTcF = QT/RR$^{0.33}$).
- Blood samples were collected after obtaining ECGs to assess vadadustat plasma concentrations.

Statistical analyses

- At each time point of ECG measurement, the placebo-corrected change from baseline QTcF (ΔΔQTcF) and 2-sided 90% confidence interval (CI) were calculated for the 3 active treatments using a linear mixed-effects model.
- The relationship between vadadustat plasma concentration and ΔΔQTcF was investigated using 3 different linear mixed-effects models. The model that fit the data best was used for predicting ΔΔQTcF at the geometric mean peak vadadustat concentration.

Results

Subject disposition and characteristics at screening

- Of the 50 subjects enrolled, 47 (94%) completed the study; 3 (6%) subjects discontinued due to withdrawal of consent or noncompliance. All 50 subjects were included in the QTc and safety analyses, and 49 were included in the PK and PK/QTc analyses.
- Mean (± SD) age and body mass index at screening were 39 ± 12 years and 26 ± 3 kg/m^2, respectively.
- The proportions of male and female subjects were similar (48% and 52%, respectively), and the majority (70%) of subjects were white.

Vadadustat pharmacokinetics

- The C_{max} and AUC values were dose proportional, while the T_{max} and $t_{1/2}$ were similar for the 2 vadadustat doses (**Table 2**).

Table 2. Vadadustat pharmacokinetics

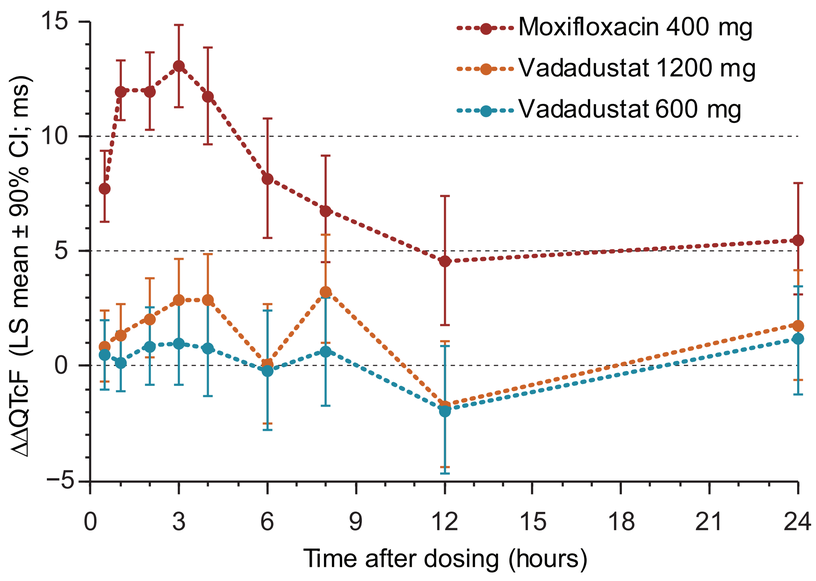
Parameter, geometric mean (CV%)*	Vadadustat 600 mg (N = 49)	Vadadustat 1200 mg (N = 49)
C_{max} (µg/mL)	53.7 (25.5)	89.3 (27.1)
$AUC_{0\text{-}t}$ (µg·h/mL)	383 (35.9)	805 (35.6)
$AUC_{0\text{-}\infty}$ (µg·h/mL)	395 (37.5)‡	849 (38.2)‡
T_{max} (h)†	3.25 (1.25–6.25)	4.25 (2.25–8.25)
$t_{1/2}$ (h)	4.95 (16.5)‡	5.48 (24.8)‡

*Except where otherwise indicated. †median (min–max); ‡N = 48. $AUC_{0\text{-}\infty}$, area under concentration-time curve extrapolated to infinity; $AUC_{0\text{-}t}$, area under concentration-time curve from time 0 to last quantifiable concentration; C_{max}, maximum plasma concentration; CV, coefficient of variation; $t_{1/2}$, apparent terminal elimination half-life; T_{max}, time to C_{max}.

Assay sensitivity

- Administration of moxifloxacin (positive control) demonstrated assay sensitivity (ie, the ability to detect clinically significant differences).
- Post-moxifloxacin least square (LS) mean ΔΔQTcF peaked at 13.1 ms at 3 hours, and the lower bound of the 90% CI was >5 ms at all 3 predefined time points (2, 3, and 4 hours; **Figure 2**), confirming assay sensitivity.

Figure 2. Effect of vadadustat on placebo-adjusted change from baseline in QTcF (ΔΔQTcF)

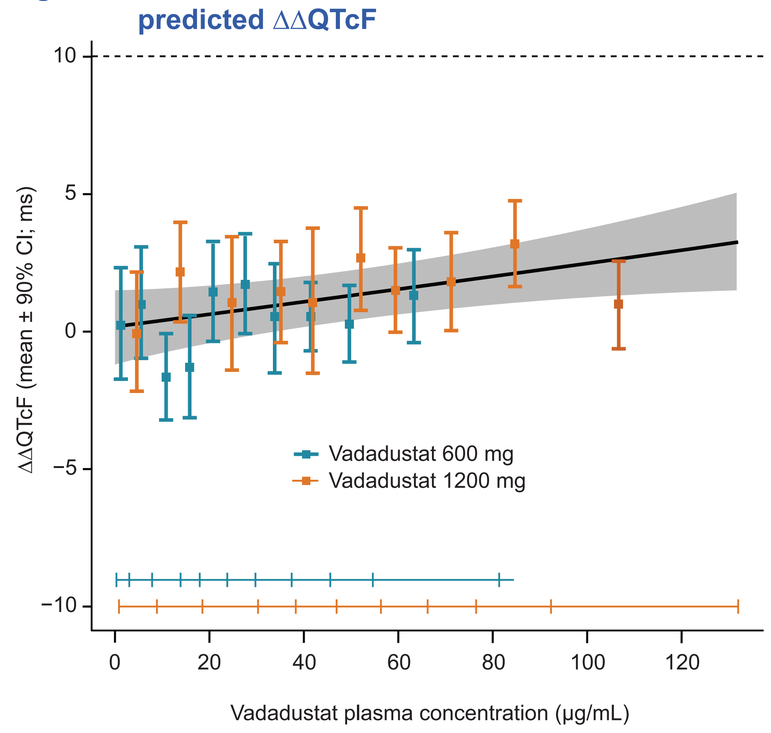


*The mean ± SD QTcF values at baseline were 406.1 ± 19.4 ms, 406.5 ± 19.1 ms, 407.0 ± 17.7 ms, and 404.7 ± 18.7 ms in vadadustat 600 mg, vadadustat 1200 mg, moxifloxacin 400 mg, and placebo groups, respectively. ΔΔQTcF, placebo-adjusted change from baseline in QTcF; CI, confidence interval; LS, least square; QTcF, Fridericia-corrected QT interval.

Effect of vadadustat on QTc and other ECG parameters

- The peak LS mean ΔΔQTcF in the vadadustat 600 mg and 1200 mg groups was 1.2 ms (90% CI: −1.2 to 3.5) at 24 hours and 3.3 ms (1.0–5.7) at 8 hours, respectively (**Figure 2**). The upper bound of the 90% CIs was well below 10 ms (**Figure 2**), the threshold level of regulatory concern as defined by the ICH E14 guideline.[1]
- Following dosing with vadadustat 600 mg, no subject had QTcF >450 ms or ΔQTcF >30 ms at any time point.
- Following dosing with vadadustat 1200 mg, 1 (2%) subject had QTcF >450 ms at 1 time point (451 ms at 3 hours), and no subject had ΔQTcF >30 ms at any time point.
- There were no clinically meaningful changes in heart rate or PR and QRS intervals.

Figure 3. Vadadustat concentration vs observed and predicted ΔΔQTcF



Red and blue squares and vertical lines represent the observed mean ΔΔQTcF and 90% CI, respectively, displayed at the median vadadustat concentration within each decile. The solid black line and gray shaded area represent the mean and 90% CI ΔΔQTcF predicted based on a linear mixed-effect model. The horizontal red and blue lines with notches show the range of plasma concentrations divided into deciles for the vadadustat 600 mg and 1200 mg doses, respectively. ΔΔQTcF, placebo-adjusted change from baseline in QTcF; CI, confidence interval; QTcF, Fridericia-corrected QT interval.

- Concentration-effect modeling yielded a slope of 0.0233 ms/µg/mL (90% CI: 0.004–0.043) (**Figure 3**). The upper bound of the 90% CI was below 10 ms at all studied vadadustat concentrations (**Figure 3**).

Safety assessments

- The frequency of adverse events (AEs) was similar among the vadadustat 600 mg and 1200 mg groups (25% and 27%, respectively), compared with 6% and 15% in placebo and moxifloxacin groups, respectively (**Table 3**).

Table 3. Frequency of adverse events

Subjects with AEs, n (%)	Placebo (N = 48)	Vadadustat 600 mg (N = 49)	Vadadustat 1200 mg (N = 49)	Moxifloxacin 400 mg (N = 48)
Any AE	3 (6%)	12 (25%)	13 (27%)	7 (15%)
AEs ≥5%*				
Nausea	0	4 (8%)	6 (12%)	1 (2%)
Diarrhea	0	4 (8%)	6 (12%)	1 (2%)
Headache	2 (4%)	4 (8%)	5 (10%)	1 (2%)
Abdominal pain	0	1 (2%)	3 (6%)	0
Dizziness	0	3 (6%)	0	1 (2%)

*Incidence of ≥5% in any group. AE, adverse event

- All AEs were mild; the most frequently reported AEs with vadadustat 600 mg and 1200 mg were nausea, diarrhea, headache, abdominal pain, and dizziness (**Table 3**).
- No serious AEs or deaths occurred in this study, and no AEs resulted in study discontinuation by the investigator.
- No AEs of torsades de pointes, ventricular tachycardia, ventricular fibrillation or flutter, syncope, or seizures were reported.
- No new safety concerns, clinically significant abnormalities or trends in clinical laboratory data, vital signs, or physical examination results were identified.

Conclusions

- This TQT study showed no clinically meaningful effect of vadadustat on cardiac repolarization in healthy subjects administered a single oral therapeutic dose (600 mg) or supratherapeutic dose (1200 mg).
- The results of this TQT study, combined with prior preclinical evidence, support the lack of proarrhythmic potential of vadadustat.

References

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CKD - Anaemia

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