A concentration–QTc analysis of vericiguat

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BACKGROUND

Vericiguat is a soluble guanylate cyclase stimulator developed for the treatment of asymptomatic–chronic heart failure (HF) in adult patients with reduced ejection fraction who are stabilised after a recent decompensation event requiring therapy.1,2 Safety evaluation of a new pharmaceutical agent should include electrocardiography (ECG) assessment to explore for potential effects on the heart rate (HR) corrected QT interval (QTc).2

Current guidelines categorise patients with coronary artery disease as having either acute or chronic coronary syndromes (CCS).2 Patients with CCS were selected for evaluation in a phase Ib trial for a dedicated QT study of vericiguat (NCT03504982), as they have fewer confounders than ECG patients with HF.2

The dedicated QT study demonstrated no clinically significant prolongation of the Fridericia-corrected QT interval (QTcF) after vericiguat 10 mg once daily at steady state in patients with CCS.2

This analysis was conducted using the International Council for Harmonisation E14 guidelines, which alter concentration–QTc (C–QTc) modelling to be used for assessing the QTc interval prolongation risk of new drugs.1,3,4

PURPOSE

To support the findings of the QT study, and, as part of an integrated risk assessment of the potential of vericiguat 10 mg to cause ventricular repolarisation, we conducted a C–QTc analysis on data from the dedicated QT study to explore the relationship between vericiguat plasma concentration and QTcF.

MATERIALS AND METHODS

QT study design

• The primary QT study was a randomised, phase Ib, placebo-controlled, double-blind, double-dummy, multicentre study (NCT03504982; Figure 1) that enrolled 74 patients with CCS.2

• Treatment: Vericiguat was dosed once daily at 2.5 mg and up to 5 mg and then to 10 mg (moxifloxacin A, B, C, respectively; over 42 ± 3 days).

• ECG: Troponic ECGs, with 2.4 min and in supine position, were recorded pre-dose and at regular intervals 1.5–7 h post-dose on Visits 1–11. Baseline ECGs were performed at Day −1 (Baseline; visit [BV]) and Day 0 (Day 0).

• Pharmacokinetics: Blood samples were collected pre-dose and at regular intervals 1.5–5 h after dosing on ECG profiles, with QTc intervals matched to pharmacokinetic measurements.

Figure 1. Study design

C–QTc modelling approaches

Two approaches for ΔΔQTc for calculations were tested: the simple baseline ΔΔQTc and the modelled baseline ΔΔQTc approach. Both models were similar with respect to their parameters and were based on ΔΔQTc from all periods with vericiguat treatment.

Testing of model assumptions

Model assumptions were evaluated as (i) absence of relevant drug effect on HR, (ii) adequacy HR correction of QTc, demonstrated by absence of correlation between HR QTc and HR, analysed by Pearson’s correlation, (ii) lack of pharmacokinetic–pharmacodynamic heterogeneity and (iv) no hints for nonlinear ΔΔQTc-F relationship.

Single baseline ΔΔQTc estimation

The modelled baseline ΔΔQTc approach, ΔΔQTc = placebo - baseline-adjusted. The latter used one baseline profile – either ‘baseline’ or ‘back baseline’ (Figure 1). Therefore, ΔΔQTc was calculated with the following model equation:

\[
\Delta\Delta QTc = \Delta QTc_{\text{observed}} - \Delta QTc_{\text{baseline}}
\]

\(\Delta QTc_{\text{observed}}\) denotes individual patients and placebo specific time-points (1.5–7 h) for the repeated treatment with Vericiguat (\(\text{Ver}_{\text{single dose}}\)) and baseline (\(\text{baseline}_{\text{single dose}}\)). Model baseline corrected QTc is same for all patients and doses. 

\(\Delta QTc_{\text{baseline}}\) denotes baseline variability and subsequent analysis was conducted on ΔΔ QTc.

C–QTc modelling

The dependencies ΔΔQTc were included in the C–QTc approach indicated a positive, but non-significant, slope (Table 1, Figure 3a).

RESULTS

• In total, 3785 C–QTc observations from 74 patients were included.

• Observed plasma concentrations for vericiguat covered up to 745 µg/l.

• Mean time intervals of more than 30 min were observed for post-dose samples and the data were considered eligible for a C–QTc model approach: 

  • In the NCT03504982, they have fewer confounders than ECG patients with HF.

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• QTc was calculated with the following model equation:

\[
\Delta\Delta QTc = \Delta QTc_{\text{observed}} - \Delta QTc_{\text{baseline}}
\]

\(\Delta QTc_{\text{observed}}\) denotes individual patients and placebo specific time-points (1.5–7 h) for the repeated treatment with Vericiguat (\(\text{Ver}_{\text{single dose}}\)) and baseline (\(\text{baseline}_{\text{single dose}}\)). Model baseline corrected QTc is same for all patients and doses. 

\(\Delta QTc_{\text{baseline}}\) denotes baseline variability and subsequent analysis was conducted on ΔΔ QTc.

• Visual inspection of ΔΔQTc versus concentration did not reveal a hysteresis effect.

• Vericiguat plasma concentration at which the upper limit of the two-sided 95% CI of the estimated ΔΔQTc was predicted to reach the 10 ms threshold (defined in the guideline) was above the observed plasma concentration associated with the therapeutic range (Figure 3).

CONCLUSIONS

• The two modelling approaches in this C–QTc analysis demonstrated: 

  • A positive relationship between ΔΔQTc and vericiguat plasma concentration that was statistically significant for the modelled baseline approach.

  • The modelled baseline ΔΔQTc approach indicated a positive and statistically significant slope (Table 2, Figure 3b).

Parameter Estimates 2.5% 97.5% 
\(\Delta\Delta QTc_{\text{observed}}\) (ms) \(-0.69\) \(-1.71\) \(0.31\)
\(\Delta\Delta QTc_{\text{baseline}}\) (ms) \(0.60\) \(2.54\) \(6.41\)
\(\sigma\) (ms) \(0.27\) \(0.23\) \(0.31\)

Table 2. Estimates from C–QTc regression based on the modelled baseline ΔΔQTc approach

• Vericiguat plasma concentration at which the upper limit of the two-sided 95% CI of the estimated ΔΔQTc was predicted to reach the 10 ms threshold (defined in the guideline) was above the observed plasma concentration associated with the therapeutic range (Figure 3).