

Supplemental Digital Content 2

Results

2.1 Evaluation of Correction Factors: QTc Evaluation Population

The study-specific correction factor was estimated using all predose QT and RR replicates from all patients in the QTc evaluation population. The study-specific QT correction factor was estimated to be 0.361, and was used to calculate the QTcS at each time point for each patient in this population. The 3 correction methods (QTcB, QTcF, and QTcS) were evaluated graphically for their relationship with RR interval (see **Fig. 1 in Supplemental Digital Content 3, which illustrates the relationship between QTc vs RR intervals using predose data for QTcS, QTcF, and QTcB in QTc evaluation population**) using pretreatment ECG data from the QTc evaluation population. QTcB and QTcF demonstrated downward and upward trends in relation to RR interval, respectively, and QTcS had a horizontal relation to the RR interval.

2.2 ECG Analysis for Safety-Analysis Population

The study-specific correction factor was estimated using all predose QT and RR replicates from all patients in the safety-analysis population. The study-specific QT correction factor was estimated to be 0.404, and was used to calculate the QTcS at each time point for each patient in this population. Similar to the QTc evaluation population, graphical analysis (see **Fig. 2 in Supplemental Digital Content 3, which illustrates the relationship between QTc vs RR intervals using predose data for QTcS, QTcF, and QTcB in safety-analysis population**) indicated that QTcS provided the best correction for the effect of heart rate on QT interval for the safety-analysis population, followed by QTcF and then QTcB. The QTcS, along with QTcF, the

predefined primary analysis endpoint of QTc, were used for QTc analysis data interpretation and conclusion. The results of the QTcB analysis were included for completeness.

Most patients (~97%) had maximum postdose QTcS and QTcF <480 ms (**see Table 1 in Supplemental Digital Content 4, which shows the categorical summary of maximum postbaseline and maximum increase from baseline of ECG parameters for safety-analysis population**) in both treatment arms. Postbaseline maximum QTcS and QTcF values ≥ 500 ms were observed in 2 (0.5%) patients and 1 (0.2%) patient, respectively, in the palbociclib plus letrozole arm. No patients had maximum postdose QTcS or QTcF values ≥ 500 ms in the placebo plus letrozole arm.

Categorical summaries of maximum postbaseline and maximum change from baseline ECG parameters are summarized in **Table 1 in Supplemental Digital Content 4**. Most patients (~92%) in both treatment arms had a change from baseline <30 ms in QTcS or QTcF. The percentage of patients with a maximum increase from baseline ≥ 60 ms in QTcS or QTcF was 0.7% and 0.5%, respectively, in the palbociclib plus letrozole arm. In the placebo plus letrozole arm, there were no patients who had a maximum increase from baseline ≥ 60 ms in QTcS or QTcF. There was no evidence of clinically significant effects of palbociclib plus letrozole or placebo plus letrozole on PR interval or QRS complex in the safety-analysis population (**see Table 1 in Supplemental Digital Content 4, which shows the categorical summary of maximum postbaseline and maximum increase from baseline of ECG parameters for safety-analysis population**).

2.3 Evaluation of Correction Factors: Exposure-Response Analysis

The study-specific correction factor was estimated using all predose QT and RR replicates from patients in the palbociclib plus letrozole treatment arm of the QTc evaluation population. The study-specific QT correction factor was estimated to be 0.351, and was used to calculate the QTcS at each time point for each patient in this dataset. The estimated slope values based on the linear relationship between baseline QTc and RR interval using QTcS, QTcF and QTcB were 0.00411, 0.0129, and -0.0717 , respectively. The slope value (0.00411) estimated between QTcS and RR interval was not significant because the 95% CI encompassed 0 (-0.00431 – 0.0125), suggesting that the strong correlation between RR and QT intervals was significantly diminished using QTcS. The slight positive slope (0.0129) observed between RR interval and QTcF suggested that the Fridericia correction factor also reduced the correlation between QT and RR intervals, but not to the same extent as that of QTcS. A negative slope (-0.0717) between RR interval and QTcB suggested that the Bazett correction factor overcorrected the correlation between RR and QT intervals. Therefore, QTcS and QTcF were the predefined primary analysis endpoints of QTc, and the QTcB results were also included for the purpose of completeness.