Supplemental Digital Content 1

Methods

1.1 Study Design and Patients

The study population included adult (≥18 years of age) postmenopausal women with proven diagnosis of adenocarcinoma of the breast with evidence of locoregionally recurrent or metastatic ER+/HER2– breast cancer not amenable to resection or radiation therapy with curative intent and not clinically indicated for chemotherapy. In addition to other exclusion criteria, patients were excluded if they had previous treatment with any CDK4/6 inhibitor, had received any agents known to be strong inhibitors or inducers of CYP3A4 or any agents known to prolong the QT interval within the last 7 days before randomization, QTc >480 ms (based on the mean value of triplicate ECGs), had family or personal history of long or short QT syndrome, had Brugada syndrome or known history of QTc prolongation or TdP, or had uncontrolled electrolyte disorders (eg, hypocalcemia, hypokalemia, and hypomagnesia) that could compound the effects of a QTc-prolonging drug.

1.2 Dose-Compliance Criteria

A PK sample is considered dose compliant if the patient received 8 consecutive days of 125 mg palbociclib QD without dosing interruption before sample collection. Additionally, for predose PK samples, the sample must have been collected 24 hours ±10% after the dose administered the day before sample collection and no more than 1 hour after the dose administered on the day of sample collection. For postdose PK samples collected on C1D14, the palbociclib dose on the day of PK sample collection must have been administered within 24 hours ±10% after the dose administered the day before sample collection to be considered dose compliant.

1.3 Analysis Populations

The results presented in this manuscript are from the QTc evaluation and safety-analysis populations.

The QTc evaluation population is a subset of patients in the QTc evaluation substudy who received at least 1 dose of study drug and had at least 1 pair of time-matched baseline (Day 0) and postbaseline (C1D14) ECG measurements. The concentration-QTc/RR analysis was performed using data from a subset of patients in the QTc evaluation population who had received at least 1 dose of palbociclib and had at least 1 pair of matching palbociclib concentration and postdose ECG measurement collected on C1D14 no more than an hour apart (matched PK-ECG pair).

The safety-analysis population comprised all patients who received at least 1 dose of any study medication and had ECG data available for evaluation.

1.4 Model Diagnostics for Exposure-Response Analysis

The plots included population predictions versus observations, individual predictions versus observations, residuals versus predictions, weighted residuals versus predictions, individual residuals versus individual predictions, weighted individual residuals versus individual predictions, a quantile probability plot (QQ) of weighted and individual weighted residuals, and a QQ plot of the random effects. Outliers were identified using the individual weighted residuals (IWRES) values exceeding ±6. In addition, a VPC for the final model was generated to evaluate whether the model provided an accurate description of the data. Simulated observations were generated for 1000 replications using the final model parameter

estimates, random effects, and the uncertainties in the fixed-effect parameters. The 2.5^{th}, 50^{th} and 97.5^{th} percentiles were summarized for each simulated dataset, binned by concentration values. The 95% CI for the predicted percentiles from the simulated data were also presented in the VPC. The same percentiles were calculated for the observed data to aid in the comparison of predictions with the observations. The actual observed data were also overlaid to indicate the distribution of data over the concentration range. The final model was used to evaluate the drug effect on QTc at the clinically meaningful target therapeutic exposure.