Cancer Chemotherapy and Pharmacology (2019) 84:621–633
https://doi.org/10.1007/s00280-019-03896-1

ORIGINAL ARTICLE

Assessment of the effect of erdafitinib on cardiac safety: analysis of ECGs and exposure–QTc in patients with advanced or refractory solid tumors

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Received: 10 May 2019 / Accepted: 14 June 2019 / Published online: 6 July 2019

Abstract

Purpose To characterize the effect of erdafitinib on electrocardiogram (ECG) parameters and the relationship between erdafitinib plasma concentrations and QTc interval changes in patients with advanced or refractory solid tumors.

Methods Triplicate ECGs and continuous 12-lead Holter data were collected in the dose escalation part (Part 1) of the first-in-human study, with doses ranging from 0.5 to 12 mg. Triplicate ECG monitoring continued in Parts 2–4 where 2 dose regimens selected from Part 1 were expanded in prespecified tumor types. Analyses of ECG data included central tendency analyses, identification of categorical outliers and morphological assessment. A concentration–QTc analysis was conducted using a linear mixed-effect model based on extracted time matching Holter data.

Results Central tendency, categorical outlier, and ECG morphologic analyses from 187 patients revealed no clinically significant effect of erdafitinib on heart rate, atrioventricular conduction or cardiac depolarization (PR and QRS), and no effect on cardiac repolarization (QTc). Concentration–QTc analysis from 62 patients indicated that the slopes of relationship between total and free erdafitinib plasma concentrations and QTcI (mean exponent of 0.395) were estimated as −0.00269 ms/(ng/mL) and −1.138 ms/(ng/mL), respectively. The predicted change in QTcI at the observed geometric mean of total and free concentration at the highest therapeutic erdafitinib dose (9 mg daily) was < 10 ms at the upper bound of the two-sided 90% confidence interval.

Conclusions ECG data and the concentration–QTc relationships demonstrate that erdafitinib does not prolong QTc interval and has no effects on cardiac repolarization or other ECG parameters.

Clinical trial registration numbers NCT01703481, EudraCT: 2012-000697-34.

Keywords Concentration–QTc modeling · ECG analysis · Erdafitinib · Holter data · Oncology · QT interval

Introduction

Many non-antiarrhythmic drugs prolong cardiac repolarization, which typically produces prolongation of the QT interval on the surface electrocardiogram (ECG), and which may produce lethal ventricular arrhythmias. An adequate premarketing investigation of the safety of a new drug candidate should include rigorous characterization of its effects on the QT interval, as described in the ICH E14 guideline [1]. This evaluation is generally performed in healthy volunteers, with placebo and positive control (such as moxifloxacin), and utilizing supratherapeutic exposures relative to the desired exposure in the target population. The effects of a new drug on the QT interval can be investigated in a dedicated study or in an early Phase 1 study by assessing

Previous presentations: Dose escalation (Part-1) data from this study was published as a manuscript in the *Journal of Clinical Oncology* (Tabernero J et al. J Clin Oncol. 2015 Oct 20;33(30):3401-8).

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00280-019-03896-1) contains supplementary material, which is available to authorized users.

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the relationship between drug plasma concentration and QT intervals, though generally requiring that supratherapeutic exposures are achieved [2–8]. The strategy and timing of QT evaluation depend on the known risk from preclinical in vitro assays and in vivo cardiovascular assessments [9].

Erdafitinib is a selective and potent oral pan-fibroblast growth factor receptor (FGFR); a tyrosine kinase inhibitor of all 4 members of the FGFR family (FGFR1–FGFR4) [10]. Recently erdafitinib received the FDA accelerated approval in the US and is now indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma that has susceptible FGFR3 or FGFR2 genetic alterations, and progressed during or following at least one line of prior platinum-containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy [11]. Erdafitinib is also in development for the treatment of other solid tumors (i.e., cholangiocarcinoma and non-small cell lung cancer) harboring certain FGFR genetic alterations. The recommended starting dose of erdafitinib is 8 mg once daily (QD), which can be titrated up to 9 mg based on individual serum phosphate levels, a biomarker of FGFR inhibition. Based on an initial study in cancer patients [12], erdafitinib pharmacokinetics (PK) were linear and time independent across doses ranging from 0.5 mg to 12 mg. Absorption was rapid, and terminal half-life was 50–60 h. Erdafitinib is highly bound to α1-acid glycoprotein, which impacts both oral clearance and volume of distribution [12].

In vitro studies performed in guinea pig right atrium, rabbit ventricular wedge preparations and human Ether-à-go-go-Related Gene (hERG), demonstrated blockage of I_{Kr} cardiac potassium channel by erdafitinib and potential pro-arrhythmic liability of the compound. The IC50 in hERG-transfected HEK293 cells was 0.41 µM (228 ng/mL), while in the rabbit ventricular wedge preparation, markers of proarrhythmia significantly increased starting at 0.1 µM (44.7 ng/mL), which is approximately 9.9-fold greater than the observed unbound geometric mean maximum serum concentration (C_{max}) of 4.51 ng/mL for the highest clinical dose of 9 mg QD. The Good Laboratory Practice (GLP) conscious oral dog study evidenced no relevant effects on any of the cardiac parameters up to a dose of 2.5 mg/kg, corresponding to an unbound C_{max} of 12.4 ng/mL, well below the IC50 for hERG inhibition. After dosing at 5 mg/kg, QT prolongation and a decrease in heart rate (HR) were noted in one dog between 30 min and 3 h after dosing.

Given the nonclinical signals summarized above, extensive cardiac safety assessments including triplicate ECG and 24-h Holter monitoring were implemented in the first-in-human (FIH) study in patients with advanced cancer who were at increased risks for cardiac complications due to their diseases, comorbidities and prior cancer treatment. An ECG cardiac safety review was conducted by a central laboratory and is summarized herein. Furthermore, to increase the robustness of evaluating the effect of erdafitinib on QTc, a concentration–response analysis using time-matched data from the 24-h Holter recording was performed to supplement the concentration–ECG analyses. The objectives of these analyses were to characterize the effects of erdafitinib on cardiac repolarization and characterize the relationships between total and free erdafitinib plasma concentrations and QT/QTc interval changes in patients enrolled in the FIH study.

Materials and methods

Study design

The FIH study of erdafitinib (ClinicalTrials.gov identifier NCT01703481; EudraCT Number: 2012-000697-34) was designed as an open-label, multicenter, 4-part study to evaluate the safety, PK and pharmacodynamics of erdafitinib in patients with advanced or refractory solid tumors and define the recommended Phase 2 dose (RP2D). In the dose escalation part (Part 1) of the study, erdafitinib was administered using a continuous daily administration regimen at doses ranging from 0.5 to 12 mg or an intermittent administration regimen at doses of 10 or 12 mg for 7 days followed by 7 days of rest (7 days on/7 days off). Two RP2Ds were selected sequentially: initially, 9 mg QD, and later, 10 mg 7 days on/7 days off. Both RP2Ds were tested in several expansion parts (Part 2 and Part 3 for daily dosing and Part 4 for intermittent dosing) in various solid tumors. Details on the study design have been previously reported [12]. The study was conducted in agreement with the Declaration of Helsinki, the ICH Good Clinical Practices guidelines and other applicable regulatory requirements.

Study population

Patients with advanced or refractory solid malignancies who were not candidates for approved or available therapies were eligible for enrollment. In Part 1, patients with any solid tumor type with or without FGFR molecular aberrations were included. In Part 2 through Part 4, patients were included if they met the molecular eligibility criteria and full study eligibility with selected types of advanced or refractory solid malignancies.

Assessments

Venous blood samples (4 mL) were collected for determination of plasma concentrations of erdafitinib predose and at 0, 1, 2, 3, 4, 6, 8, and 24 h on day 1 of cycles 1 and 2, and predose only on day 1 of cycle 3. Plasma concentrations

of erdafitinib were determined using a validated nonchiral liquid chromatography–mass spectrometry (LC–MS/MS) assay within the concentration range of 1–2000 ng/mL. To account for the difference in free erdafitinib concentrations due to differences in α-1 acid glycoprotein between patients, free fraction was determined either in predose plasma samples fortified with erdafitinib at 100 ng/mL, and/or in non-fortified postdose samples and analyzed by equilibrium dialysis. Concentrations in buffer were determined using a qualified LC–MS/MS assay. Free erdafitinib plasma concentration was calculated using measured free fraction and total erdafitinib plasma concentration. In case of a missing free fraction, free erdafitinib plasma concentration was considered as missing.

During the conduct of the study, both ECG and 24-h Holter files were collected, measured and interpreted by eResearch Technology Inc. (ERT; Philadelphia, PA, US), a centralized ECG core laboratory. The triplicate ECGs were collected at the following timepoints with matching erdafitinib concentrations: in all cohorts at screening, on cycle 1 day 1 predose and 2, 4, and 8 h postdose, cycle 1 day 7 (intermittent dosing) or 8 (daily dosing) predose and 2 and 4 h postdose, and cycle 2 day 1 predose and 2, 4, and 8 h postdose (postdose in Part 1 only). The timing of ECGs and matching PK data are summarized in Supplemental Table 1. A high-resolution semi-automated on-screen caliper method with annotations placed on 3 consecutive beats on a single lead (usually lead II) was used for ECG reading. The ECG reader was blinded to patients and their treatment.

In addition to ECG assessments, 24-h Holter monitoring was performed during Part 1 of the study at screening (baseline day), and on day 1 of cycles 1, 2, and 3: triplicate 10-s ECGs were extracted predose and at 1, 2, 3, 4, 6, 8, and 24 h after erdafitinib dosing on day 1 of cycle 1 and cycle 2, and predose only on day 1 of cycle 3 to match PK measurements.

PK/ECG measurements on cycle 2 day 1 were considered as primary assessments, rather than after single dose (cycle 1 day 1), since steady-state erdafitinib plasma concentrations were expected to be achieved by that time. Thus, the clock times of PK/ECG measurements on cycle 2 day 1 were used as references for extraction of matching screening ECG values to derive individual time-matched QTc change from baseline (ΔQTc). To match ECG measurements on other visits, the same screening values extracted based on the clock time of the ECG measurements on cycle 2 day 1 were used if they had a difference of less than 1 h compared with the clock time of the ECG measurements on cycle 1 day 1 or cycle 3 day 1. If no screening value for cycle 2 day 1 could match the clock time (within 1 h) of a specific timepoint for cycle 1 day 1 or cycle 3 day 1, then additional screening values with a matching clock time were extracted. In case no Holter measurements were available on cycle 2 day 1, screening values matching the clock time on cycle 1 day 1 were extracted and used as baseline.

Analysis of ECG parameters

Analyses of ECG data included, evaluation by timepoint of the change from baseline for all ECG parameters (HR, PR, QRS, QT, Fridericia's [QTcF] and Bazett's [QTcB] corrections), categorical outlier analyses, and analyses of new ECG morphologic findings. The ECG analyses included ECG data for all patients enrolled in the trial who had at least one available centrally evaluated baseline and on-treatment ECG.

Due to the variations in dose, dosing schedules and ECG collection schedules between the various parts of this trial, data were analyzed and reported in 3 groups: Part 1 (each cohort separately and 2 pooled groups: continuous dosing and intermittent dosing), Part 2 and Part 3 (continuous dosing) and Part 4 (intermittent dosing).

Central tendency analysis

The ECG analysis was based on defining the central tendency of all ECG interval parameter changes as a change from baseline. For central tendency and outlier analyses, the baseline was defined as the mean of the ECG measurements from the triplicate ECGs recorded predose at cycle 1 day 1. Only data from timepoints at which ECG data were available for at least 5 patients were utilized for the timepoint analysis.

The following criteria were used to define outlier for each ECG parameter, by patient and timepoint:

- HR < 50 bpm and ≥ 25% decrease from baseline, or HR > 100 bpm and ≥ 25% increase from baseline.
- PR interval > 200 ms and ≥ 25% increase from baseline.
- QRS interval > 100 ms and ≥ 25% increase from baseline.
- Postdose QTcF interval > 500 ms and baseline ≤ 500 ms; > 480 ms and baseline ≤ 480 ms; and QTcF changes from baseline of > 30–60 ms and > 60 ms.

Morphological analysis

Morphological analyses were performed by the central ECG laboratory cardiologist by comparing each patient's on-treatment ECGs with baseline morphology to the baseline and Screening ECGs. "New" findings were defined by the presence of an ECG abnormality on one or more on-treatment ECG that was not present on any pre-treatment ECG.

Analysis of Holter data

Exploratory analysis

Fridericia's (QTcF) and Bazett's (QTcB) corrections were evaluated, as well as QT correction methods involving an estimation of the exponent at a population (QTcP) or at an individual level (QTcI) [1, 13]. The most appropriate correction method, based on the lack of statistical significance of the slope between QTc and HR, was used for the concentration–QTc analysis. As diurnal variation in QTc has been previously reported, the QTc data at screening were evaluated as a function of clock time to explore the presence of a circadian rhythm [14–16].

The key assumption underlying the analysis model was the direct effect of erdafitinib plasma concentrations on the ΔQTc, which implies the absence of hysteresis, i.e., no time-delay between erdafitinib plasma concentrations and ΔQTc [17]. This assumption was assessed by graphical inspection of mean and individual profiles for ΔQTc and erdafitinib plasma concentrations over time, as well as individual plots representing the time ascending observed QTc (or ΔQTc) versus erdafitinib plasma concentrations. A direct effect of erdafitinib was considered: if no anticlockwise loop was observed from the individual hysteresis plots, and if the time difference between the median time at which the maximum observed erdafitinib plasma concentration was reached (t_{max}) and the time at which the highest ΔQTc response was observed (U_{max}) was less than 1 h and not statistically different at the 1% level.

Concentration–QTc analysis

The relationship between erdafitinib plasma concentrations and ΔQTc was evaluated using a linear mixed-effects model, as recently described [4, 6, 8, 17] and conducted in R (Version 3.3.2; Comprehensive R Network, http://cran.r-project.org/). The model included ΔQTc as the dependent variable, and the independent variables were the erdafitinib plasma concentration (Cp) (total or free) as a continuous covariate and each nominal postdose timepoint (time_i) as categorical factors, as described in Eq. 1:

$$\Delta QTc \sim \left(\text{intercept} + \eta_{\text{int}}\right) + \gamma_i * \text{time}_i + \left(\beta_1 + \eta_{\text{slp}}\right) * Cp + \varepsilon,$$

where η was the random inter-individual variability, assumed to be independent and normally distributed with mean of zero and variance equal to ω^2 and ε was the random residual variability, assumed to be an additive independent and normally distributed random variable with mean of zero and variance equal to σ^2. The appropriateness of the inclusion of random slope (η_{slp}) and random intercept (η_{int}) in the model was tested by fitting models without random effects to the data.

The linearity of the concentration–QTc relationship was evaluated by visual inspection of relevant goodness-of-fit plots from a linear mixed-effect model, followed by statistical testing. A model with an empirical quadratic term in concentration was fitted and the significance of the quadratic term tested at the two-sided 5% alpha level. In case of the absence of trends in the goodness-of-fit plots and a non-significant quadratic term, the concentration–QTc relationship was considered linear.

From the model, the slope was estimated with its two-sided 90% CI calculated using the asymptotic standard error on this parameter.

For the concentration–QTc analyses, the predicted effect of erdafitinib on ΔQTc was estimated at the observed C_{max} geometric mean at steady state following the continuous administration of 9 mg QD (1911 ng/mL and 4.51 ng/mL for total and free concentrations, respectively) and was calculated as the product of the slope estimate and the observed C_{max} geometric mean. To exclude a QT effect of concern for erdafitinib, the upper bound of the two-sided 90% CI of the model-predicted mean ΔQTc had to be lower than 20 ms (threshold typically accepted for oncology drugs [18]), at the geometric mean C_{max} at steady state obtained after administration of the clinically relevant dose of 9 mg daily.

Results

In total, 187 patients with advanced or refractory solid tumors participated in the FIH study and had ECG measured; 66 patients in Part 1 received continuous daily doses ranging from 0.5 to 12 mg QD or intermittent doses of 10 and 12 mg 7 days on/7 days off; 11 patients in Part 2 received either 6 or 9 mg QD, 46 patients in Part 3 received 9 mg QD, and 64 patients in Part 4 received 10 mg 7 days on/7 days off. Of the 66 patients from Part 1, 62 patients participated in the Holter analysis. Table 1 summarizes the demographic and baseline characteristics of the patients included in the ECG and Holter analyses.

ECG analysis

Results of the mean time average analysis are shown in Table 2. There were no clinically relevant changes for any of the ECG parameters (HR, PR, QRS, QTcF, QTcB). A plot of mean change from baseline over time is shown in Fig. 1 for patients enrolled in Part 1 of the study. The timepoint data showed no clinically significant effect of erdafitinib on cardiac repolarization. In the timepoint analysis, the peak magnitude for the QTcF change from baseline ranged from − 17.4 to 5.8 ms across all cohorts and timepoints, with the

Table 1 Summary of demographic and baseline characteristics

Patient characteristic		ECG analysis *N* (%) or mean (SD) [range]	Holter analysis *N* (%) or mean (SD) [range]
Total N		187	62*
Part/dose group	Part 1	66	
	0.5 mg (daily)	3	3 (4.8)
	2 mg (daily)	4	4 (6.5)
	4 mg (daily)	7	7 (11.3)
	6 mg (daily)	9	9 (14.5)
	9 mg (daily)	9	9 (14.5)
	10 mg (intermittent)	14	11 (11.3)
	12 mg (daily)	7	7 (11.3)
	12 mg (intermittent)	13	12 (19.4)
	Part 2	11	NA
	Part 3	46	NA
	Part 4	64	NA
Dose regimen	Continuous daily	96	39 (62.9)
	Intermittent	91	23 (37.1)
Gender	Female	107 (57.2)	35 (56.5)
	Male	80 (42.8)	27 (43.5)
Race	White	170 (90.9)	60 (96.8)
	Black or African American	4 (2.1)	0 (0)
	Asian	5 (2.7)	2 (3.2)
	Unknown/not reported	8 (4.3)	0 (0)
Cancer type**	Breast	36 (19.3%)	7 (11.3)
	Urothelial	30 (16.0%)	8 (12.9)
	Non-small cell lung cancer	24 (12.8)	2 (3.2)
	Colorectal	11 (5.9)	10 (16.1)
	Other	75 (40.1)	40 (64.5)
Age (years)		57.7 (12.02) [21, 84]	56.5 (10.8) [32; 81]
Weight (kg)		69.9 (16.23) [36, 132]	69 (14.9) [35.9; 109]
FU (%)		0.35 (0.21) [0.080–1.50]	0.37 (0.19) [0.12; 0.83]*

*2 patients included in the analysis based on total concentrations ($N=62$) were not included in the analysis based on free concentrations ($N=60$) as they did not have FU values. Reported FU is the first available FU

**Only cancer types present for at least 5 subjects are reported. Other cancer types are grouped under "Other"

FU fraction unbound; *SD* standard deviation

Table 2 Summary of time-averaged analysis of ECG parameters

Parameter	Part 1 pooled daily dosing cohorts (0.5–12 mg QD)	Part 1 pooled intermittent dosing cohorts (10 or 12 mg 7 days on/7 days off)	Parts 2 and 3 (9 mg QD)	Part 4 (10 mg 7 days on/7 days off)
Total *N*	39	27	56	64
HR tachycardic outliers, *n* (%)	2 (5)	0	1 (2)	6 (9)
HR bradycardic outliers, *n* (%)	0	0	0	0
PR outliers, *n* (%)	0	0	0	0
QT new > 500 ms, *n* (%)	0	0	0	0
QTcF new > 500 ms, *n* (%)	0	0	0	1 (2)
QTcF new > 480 ms, *n* (%)	0	0	1 (2)	1 (2)
QTcF > 30–60 ms increase, *n* (%)	3 (8)	4 (15)	4 (7)	9 (14)
QTcF > 60 ms increase, *n* (%)	0	0	0	0
QTcB new > 500 ms, *n* (%)	0	0	1 (2)	1 (2)

bpm beats per minute; *ECG* electrocardiogram; *HR* Heart rate; *ms* milliseconds; *N* total number of patients; *n* number of patients in a subgroup; *QTcB* Bazett correction; *QTcF* Fridericia correction

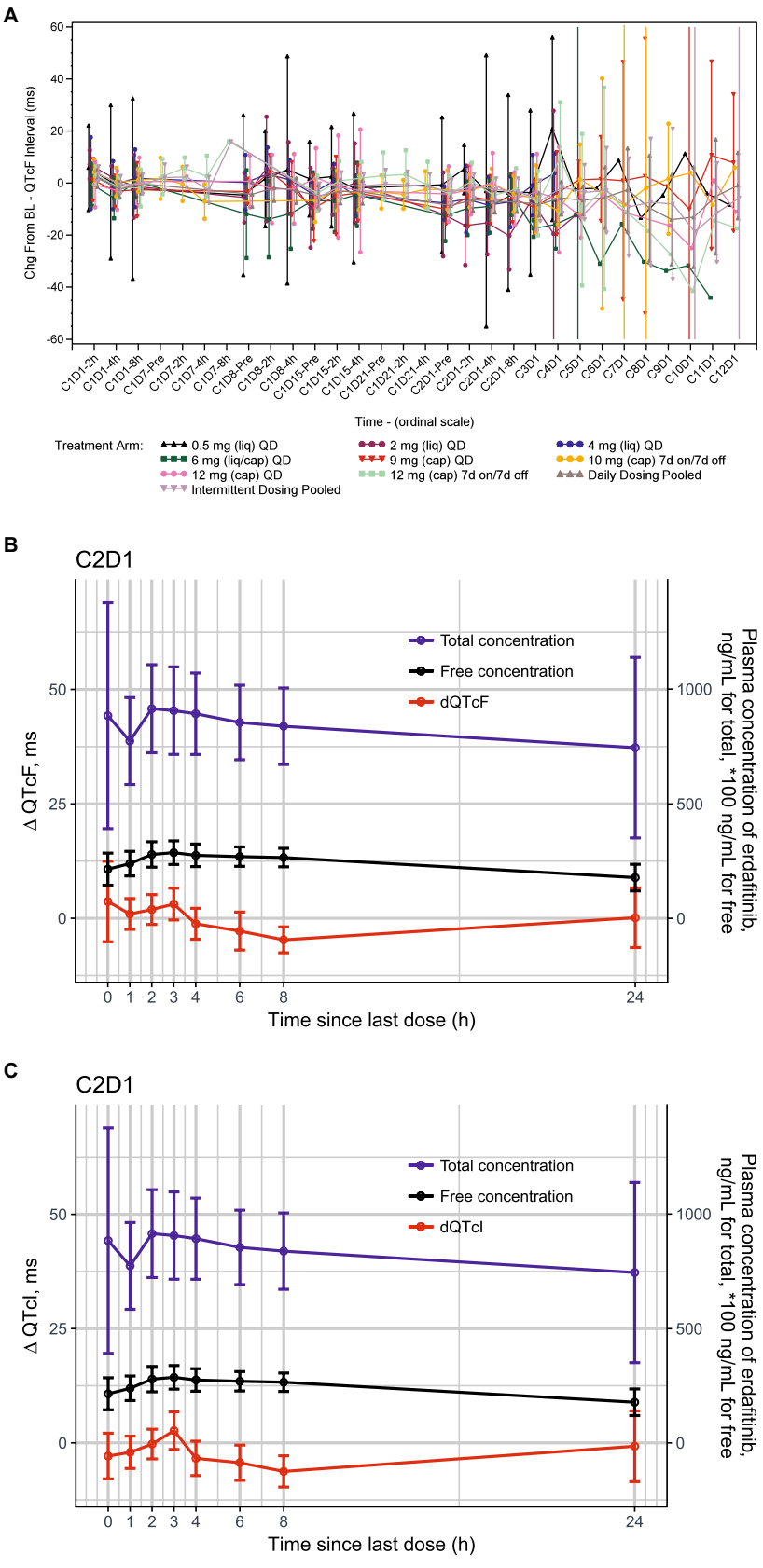


Fig. 1 **a** Mean change from baseline in QTcF by timepoint; **b** mean change from baseline in QTcF or **c** QTcI, total and free plasma concentrations of erdafitinib versus time since last dose at cycle 2 day 1 (Holter analysis dataset) C2D1 cycle 2 day 1; CI confidence interval; ms milliseconds; h hour; QD once daily; QTcF Fridericia correction; QTcI individual-specific QT correction. Points represent means and error bars, the 90% CI around the means

lowest mean value observed in the 6 mg QD (cycle 3 day 1, postdose) and highest mean value observed in the 12 mg intermittent dose groups (cycle 1 day 7, 2 h after dosing).

In the outlier analysis, no patients had a > 60 ms increase in QTcF; only 1 patient in the 10 mg intermittent dosing group (Part 4) had a new QTcF > 500 ms. Two patients had a new QTcF > 480 ms. No patients developed new ST or T wave changes suggestive of coronary ischemia or infarction, abnormal U waves, or new conduction block. One patient in the 12 mg intermittent dosing group (Part 1), a 65-year-old male with lung cancer metastatic to the pericardium as well as to multiple other organs, developed atrial bigeminy at 4 h postdose on cycle 1 day 1, followed by new atrial flutter with 2:1 atrioventricular block at 8 h postdose.

Analysis of Holter-extracted ECG data

The analysis based on total erdafitinib concentrations included 62 patients with 704 paired PK and Holter ECG with matching baseline. A total of 1142 Holter ECG measurements were used with 438 ECGs included as baseline time-matched (screening), and 375, 324, and 5 ECGs obtained on cycle 1, cycle 2, and cycle 3, respectively. For the analysis based on free drug concentrations, 60 patients with 685 paired PK and Holter ECG with matching baseline were available. The number of Holter ECG measurements at baseline, cycle 1, cycle 2, and cycle 3 were 424, 362, 318, and 5, respectively. Observed concentrations ranged up to 4890 ng/mL and 11 ng/mL for the analysis based on total and free concentrations, respectively.

QT measurements at baseline and postdose were plotted as a function of HR to visualize the existing relationship (Fig. 2a). The effect of Fridericia's correction at baseline and postdose for all patients was evaluated (Fig. 2b). Fridericia's correction was not sufficient to fully correct for HR, since a significant slope between QTcF and HR still existed ($p < 0.001$). Thus, QTcP and QTcI (Fig. 2c) were also explored. The population correction exponent was estimated at 0.410, whereas the mean of the individualized exponents was estimated at 0.395 (with a SD quantifying the between-patient variability of 0.0151). A significant slope still existed between QTcP and HR ($p < 0.01$), whereas the slope between QTcI and HR was not significant. Since no significant trend was seen between QTcI and HR, QTcI was selected as the primary response variable.

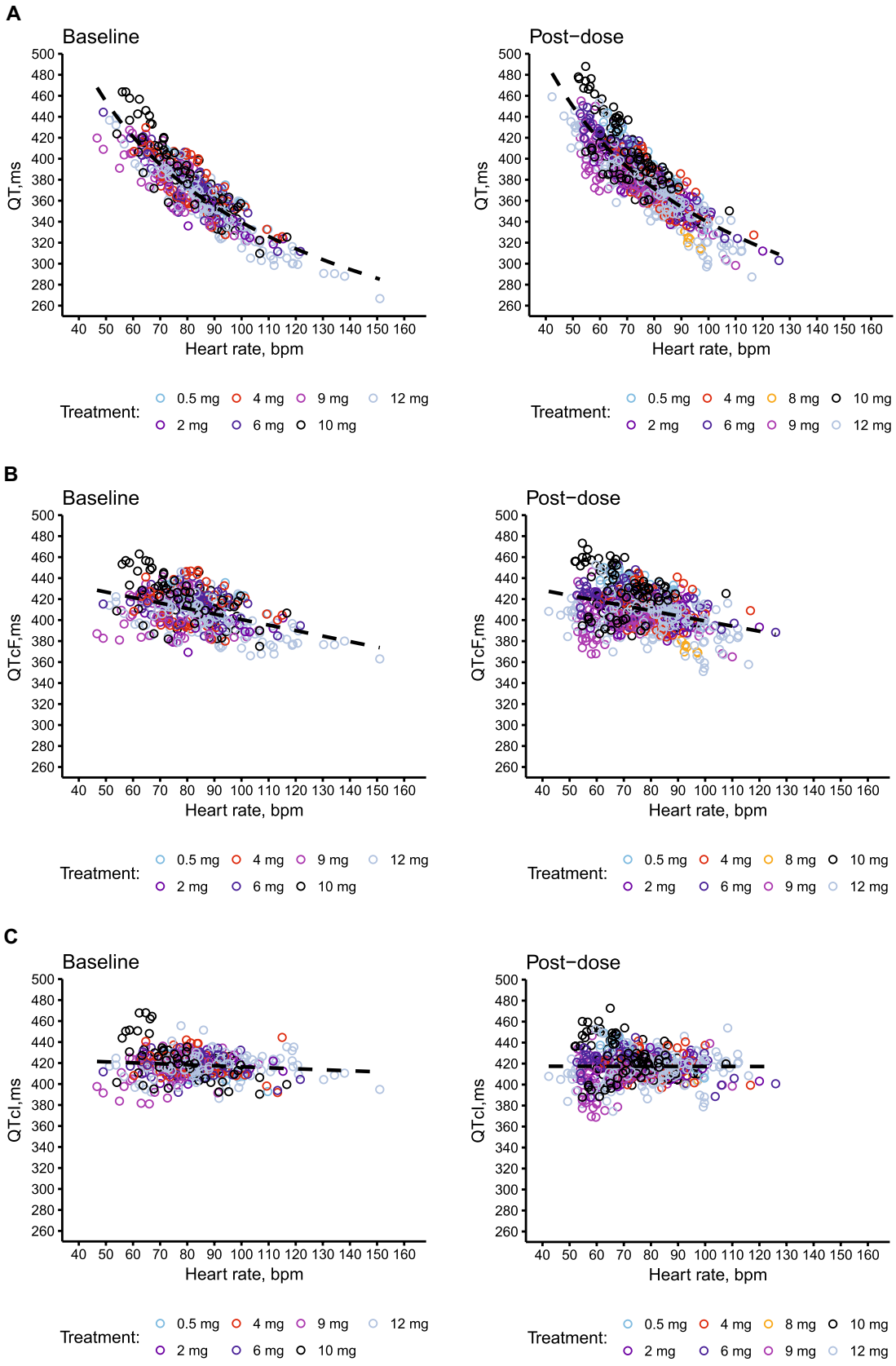
There was no evidence of a relationship between QT, QTcF or QTcI and clock time at screening (Supplemental Figure 1). It was nevertheless decided to formally test the effect of time in the concentration–QTc analysis. The appropriateness of a direct effect of erdafitinib concentration on the ΔQTcI was confirmed graphically for both total and free erdafitinib concentrations. Mean plots of ΔQTcI versus time since last dose are overlaid with plots of total and free mean plasma concentrations of erdafitinib in Fig. 3.

The presence of an anticlockwise loop was not evident from the observation of the individual hysteresis plots and no delay was seen between t_{max} and U_{max}. Furthermore, t_{max} and U_{max} were not statistically different for cycle 1 day 1 and cycle 2 day 1 both for total (p value of 0.926 and 0.896, respectively) and free concentrations (p value of 0.943 and 0.872, respectively). The appropriateness of using a linear model was also confirmed graphically: no trend was seen in the normal QQ-plots of the residuals, nor in the plots of residuals versus erdafitinib plasma concentrations or versus ΔQTcI, and the residuals showed normal random scatter around zero or the identity line. Furthermore, adding a quadratic term in the exposure–response model did not significantly improve the model fit for both total ($p = 0.371$) and free ($p = 0.079$) erdafitinib plasma concentrations.

Thus, a linear mixed-effect model was fitted to the data with ΔQTcI as dependent variable, erdafitinib plasma concentrations as continuous independent variable, and each $time_i$ as categorical covariate. The direct linear relationships between ΔQTcI and total and free erdafitinib concentration are shown in Fig. 3. While the inclusion of a random intercept term improved model fit for both total and free concentration models, the addition of a random effect on the slope of the erdafitinib plasma concentration effect was not significant for either model. The estimated parameters of the final model for total and free erdafitinib plasma concentrations are shown in Table 3. Model parameters were reported with 95% CI to evaluate their significance in the model. The slopes for total and free erdafitinib plasma concentrations were the only significant parameters and indicated that increases in erdafitinib plasma concentrations resulted in decreased ΔQTcI. The timepoint effects were not significant, suggesting that having a time-matched baseline was sufficient to capture the circadian rhythm.

The slopes of the relationship between total and free erdafitinib plasma concentrations and QTc interval were estimated as − 0.00269 and − 1.138 ms/(ng/mL), respectively. Similar estimates were noted when the analysis was conducted using ΔQTcF with a slope of − 0.00229 and − 0.992 ms/(ng/mL) for the relationship with total and free concentrations, respectively.

The model-predicted mean ΔQTcI at the observed geometric mean C_{max} of erdafitinib for total (1911 ng/mL) and free (4.51 ng/mL) plasma concentration at steady state following a therapeutic 9 mg QD dose were − 5.1 ms (90% CI − 8.8, − 1.5 ms) and − 5.1 ms (90% CI − 8.3, − 2.0 ms), respectively.


A
Baseline
Post−dose
QT,ms
Heart rate, bpm
Treatment:
0.5 mg
2 mg
4 mg
6 mg
8 mg
9 mg
10 mg
12 mg
B
QTcF,ms
C
QTcI,ms

◂**Fig. 2** **a** QT, **b** QTcF and **c** QTcI versus HR at Baseline and Postdose. The dotted lines represent the prediction from non-linear regression analysis of QT, QTcF or QTcI vs. HR (HR = 60/RR). CI confidence interval; HR Heart rate; ms milliseconds; QTcI individual-specific. QT correction; QTcF Fridericia correction

Discussion

Given the in vitro signal observed on the effect of erdafitinib on QTc prolongation, extensive cardiac assessments including triplicate ECG and continuous 12-lead Holter recordings were implemented as part of the FIH study. Central tendency, categorical outlier, and ECG morphologic analyses revealed no clinically significant effect of erdafitinib on HR, or on atrioventricular conduction or cardiac depolarization as measured by the PR and QRS intervals, and no effect on cardiac repolarization (QTc). One patient with pericardial infiltration by his malignancy developed new atrial flutter.

To ensure a robust evaluation of the effect of erdafitinib on QTc, a concentration–response analysis was conducted. Indeed, the evaluation of the effect of a new oncologic agent on cardiac repolarization is often challenging. Due to the toxicity of such agents, the evaluation of a new drug's ECG effects often takes place during patient trials, without placebo and positive control, and with limited ability to control the many factors increasing QTc variability (e.g., underlying disease, prior treatment with cardiotoxic agents). These considerations make it extremely difficult to conduct a patient trial with adequate power to exclude a 5–10 ms QTc prolongation using a by timepoint analysis, as described in the initial version of the ICH E14 guidance [19].

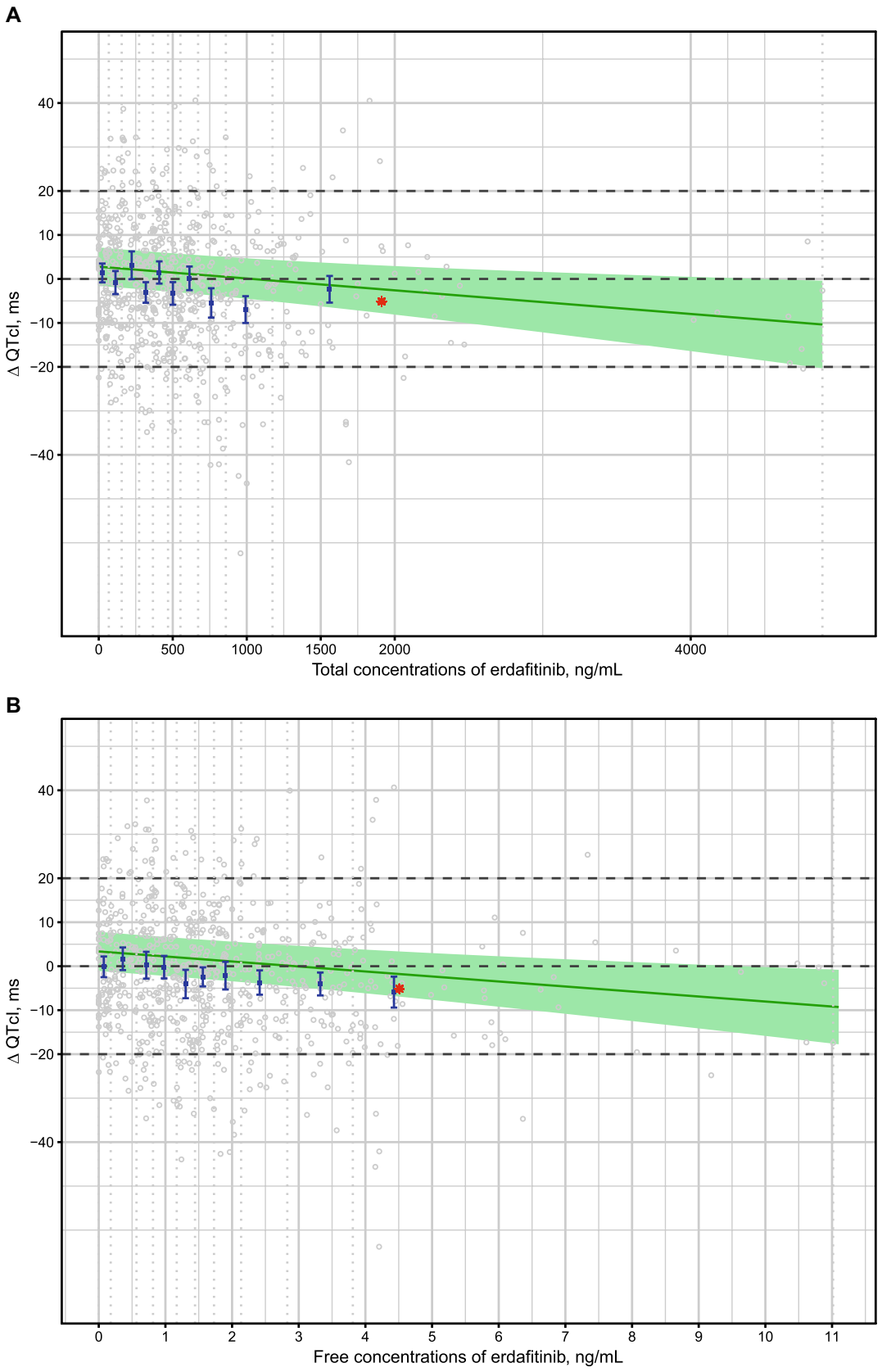
The use of concentration–QTc modeling has been advocated as a more efficient assessment of a drug candidate's potential to cause QTc prolongation, and is now accepted as an alternative to the standard by timepoint analysis [1]. For erdafitinib, triplicate ECGs for the timepoint analysis were collected at a limited number of timepoints (0, 2, 4, and 8 h) and lacked time-matched baseline. Concentration–QTc analysis, based on additional Holter-extracted ECGs, was therefore utilized to supplement the evaluation of erdafitinib's effect on cardiac repolarization. Supratherapeutic exposures of erdafitinib (12 mg QD) were included in this study, which is uncommon in the oncology setting [17]. The highest corresponding exposure included in the analysis was 4890 ng/mL and 11 ng/mL for total and free erdafitinib concentrations, respectively, 2.6- and 2.4-fold above the observed mean C_{max} at the recommended clinical dose of 9 mg.

The concentration–QTc analysis was conducted based on both total and free erdafitinib, as erdafitinib is highly bound to plasma proteins with an average free fraction of 0.37%. The ratio of the slopes for total and free erdafitinib plasma concentrations was 0.0024, generally consistent with the observed free fraction. Assessment of QTc potentials based on free erdafitinib concentrations was critical to account for differences in protein binding between animal species. The signal observed in the GLP dog study corresponded to total and free maximum erdafitinib concentrations of 90.2 and 12.4 ng/mL, respectively. Dogs have a higher free fraction (circa 13%) relative to humans (0.37%), making it misleading to assess the QT prolongation risk based on the total exposure.

As no placebo comparator could be included in this patient trial, a full 24-h baseline Holter recording was collected prior to erdafitinib dosing, from which time-matched baseline ECGs could be extracted. This adjustment for time-matched baseline measurements was expected to reduce the influence of inter-patient differences and to account for potential diurnal effects, such as those due to circadian rhythm and/or the impact of a meal, which increases the power of the concentration–QT analysis to exclude small mean QTc effects [20]. The effect of the timepoints on QTc was found to be not significant in the linear mixed-effects model, suggesting that using a clock time-matched baseline was able to minimize the diurnal variation in QTc [21]. In this study, for QTc timepoints at cycle 1 day 1 and cycle 3 day 1, using the baseline previously extracted for the corresponding timepoints at cycle 2 day 1 was preferred, allowing until 1-h difference with the available baseline value. It appears that allowing a 1-h difference for time matching with the baseline still allows correction for diurnal variation and can help reducing the number of ECG extractions necessary to conduct this type of analysis.

Appropriate correction of the QT interval for changes in HR is essential for the evaluation of drug-induced QT prolongation, since inadequate correction can result in artificial conclusions [1, 13, 22, 23]. In this analysis, the Fridericia correction did not fully account for the HR effect on QTc. Thus, other corrections (QTcP and QTcI) were evaluated. Non-linear regression analysis showed similar estimations of the correction factor at baseline (drug-free period) and postdose and was thus estimated using both baseline and postdose data. The estimates of the correction exponent from population and individualized correction fell between the correction factors established by Fridericia and Bazett. Since no significant trend was seen between QTcI and HR both at baseline and postdose, QTcI was selected as the primary response variable. The individualized correction was considered suitable since a sufficient number of ECG data in each patient was collected over a reasonable period of time (24 h), thus leading to a sufficient broad range of observed HR to estimate the individual correction factor.

Data in patients with cancer may also be more variable as standardization of the ECG/Holter assessments may be more difficult in this population (e.g., meal restrictions, concomitant medications, etc.). A threshold of 20 ms is thus typically accepted to define a clinically significant QTc signal


A
Δ QTcI, ms
40
20
10
0
−10
−20
−40
0
500
1000
1500
2000
4000
Total concentrations of erdafitinib, ng/mL
B
Δ QTcI, ms
40
20
10
0
−10
−20
−40
0
1
2
3
4
5
6
7
8
9
10
11
Free concentrations of erdafitinib, ng/mL

◂**Fig. 3** Relationship between ΔQTcI and erdafitinib **a** total and **b** free plasma concentrations. Solid green line (+shaded area): model-predicted mean ΔQTcI (+90% CI including uncertainty on the slope estimate). Blue boxes (+vertical bars): observed arithmetic means (+90% CI) for the ΔQTcI within each plasma concentration decile. Red star represents ΔQTcI predicted for the geometric C_{max} at steady state of a 9-mg once daily dose (1911 ng/mL for total concentrations and 4.51 ng/mL for free concentrations). Observed ΔQTcI were corrected by the estimated individual intercept and the effect of each timepoints, which were not considered to be related to the plasma concentration effect of erdafitinib (absolute value of correlations < 0.2). CI confidence interval; ms milliseconds; QTcI individual-specific QT correction

for oncology drugs [18]. A negative slope between ΔQTcI and erdafitinib total or free plasma concentration was estimated. The two-sided 90% upper CI of the change in QTcI at the observed erdafitinib geometric mean C_{max} at steady state following a 9-mg QD dose was -1.5 and -2.0 ms for total and free erdafitinib concentrations, respectively, well below the threshold of 20 ms. In addition, these estimated effects were also lower than the commonly accepted threshold of 10 ms for non-oncology drugs, thus excluding any clinically significant effect of erdafitinib on QTcI after multiple daily doses of the 9 mg therapeutic dose.

A concentration–QTc analysis was also conducted using the resting 12-lead ECGs and using a time-averaged ECG baseline (one set of triplicate ECGs collected predose on day 1) instead of the Holter data. The slopes were not statistically significant and the ΔQTc at the upper limit of the two-sided 90% CI were 1.05 and 0.99 ms, respectively, for analysis of total and free concentrations. These conclusions are consistent with the current concentration–QTc analysis using the Holter-extracted 12-lead ECGs and using a time-matched baseline.

In conclusion, the analysis of the ECG data and the concentration–QTc interval relationships revealed that erdafitinib did not prolong QTc interval and had no effects on cardiac repolarization or other ECG parameters. These analyses

Table 3 Final parameter estimates for the concentration–QTc model with erdafitinib plasma concentrations and ΔQTcI

	Estimate	Lower limit 95% CI[a]	Upper Limit 95% CI[a]	Pr(>|t|)[b]
Total plasma concentration				
Intercept (ms)	2.783	−2.413	7.975	0.297
Slope (ms/(ng/mL))	−0.00269	−0.00498	−0.000387	0.0229
Timepoint 1 h (ms)	−0.469	−6.223	5.308	0.874
Timepoint 2 h (ms)	1.171	−4.625	6.995	0.694
Timepoint 3 h (ms)	0.469	−5.291	6.262	0.874
Timepoint 4 h (ms)	−4.196	−9.885	1.521	0.151
Timepoint 6 h (ms)	−3.529	−9.173	2.143	0.224
Timepoint 8 h (ms)	−2.396	−8.028	3.264	0.408
Timepoint 24 h (ms)	−2.810	−9.971	4.373	0.445
Free plasma concentration				
Intercept (ms)	3.355	−1.941	8.646	0.217
Slope free (ms/(ng/mL))	−1.138	−1.968	−0.308	0.00813
Timepoint 1 h (ms)	−0.473	−6.295	5.365	0.874
Timepoint 2 h (ms)	0.796	−5.080	6.688	0.792
Timepoint 3 h (ms)	0.720	−5.119	6.582	0.810
Timepoint 4 h (ms)	−4.405	−10.165	1.375	0.137
Timepoint 6 h (ms)	−3.165	−8.879	2.568	0.281
Timepoint 8 h (ms)	−2.645	−8.344	3.073	0.366
Timepoint 24 h (ms)	−3.056	−10.234	4.135	0.408

Pr(>|t|): *p* value

CI confidence interval; *ms* milliseconds

[a]Model parameters were reported with a 95% CI for significance in the model

[b]Calculated with Kenward–Roger approximations to degrees of freedom

supported a reduced number of ECG monitoring timepoints in Phase 2 and Phase 3 studies.

Acknowledgements Authors thank the study participants, without whom this study would never have been accomplished, and all the investigators, their medical, nursing and laboratory staff for their participation in this study. Erdafitinib (BALVERSA™, JNJ-42756493) was discovered in collaboration with Astex Pharmaceuticals. The authors also thank Dr. Himabindu Gutha (SIRO Clinpharm Pvt. Ltd.) for writing assistance, Dr. Harry Ma (Janssen Research & Development, LLC) for additional editorial support and Frederic Saad for helping with the creation of the dataset.

Study support: Janssen Research & Development, LLC, USA.

Author contributions Hong Xie, Juan José Perez-Ruixo, Daniele Ouellet: conception and design; Elodie Valade, Anne-Gaëlle Dosne, Hong Xie, Daniele Ouellet: collection and assembly of data; Elodie Valade, Anne-Gaëlle Dosne, Hong Xie, Robert Kleiman, Lilian Y Li, Juan José Perez-Ruixo, Daniele Ouellet: data analysis and interpretation. Dr. Kleiman is an employee of eResearch Technology Inc. (ERT), Philadelphia. All other authors are/were employees of Janssen Research & Development and shareholders in the parent company (Johnson & Johnson).

All authors participated in the original design of the studies, supervising recruitment and monitoring of data quality, and contributed to the data interpretation, development and review of this manuscript and confirm that they have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. All authors meet ICMJE criteria and all those who fulfilled those criteria are listed as authors. All authors had access to the study data, provided direction and comments on the manuscript, made the final decision about where to publish these data and approved submission to this journal.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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