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ORIGINAL ARTICLE

Effect of lenvatinib (E7080) on the QTc interval: results from a thorough QT study in healthy volunteers

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Abstract
Purpose QT assessment of oncology drugs is generally challenging because they are genotoxic and, of necessity, they require multisite evaluation in cancer patients. Lenvatinib is not genotoxic, therefore, this thorough QT (TQT) study with lenvatinib, a multityrosine kinase inhibitor, was undertaken utilizing healthy volunteers and concentration-effect modeling to project the TQT effect at high plasma levels.
Methods Fifty-two healthy subjects randomly received single doses of lenvatinib 32 mg, placebo, or moxifloxacin 400 mg in a three-way crossover study. Serial electrocardiograms were recorded, and the effect on placebo-corrected change-from-baseline QTcF (ΔΔQTcF) was evaluated. The relationship between lenvatinib plasma concentrations and QTcF was analyzed with linear mixed-effects modeling.
Results Lenvatinib mildly lowered the heart rate by 5–8 bpm during the first 12 h after dosing. ΔΔQTcF was shortened with a peak effect of −5.72 ms (90 % confidence interval (90 % CI) −7.76 to −3.69 ms) at 6 h postdosing. The upper bound of mean ΔΔQTcF did not exceed 2 ms at any time point postdosing. A concentration-dependent effect of lenvatinib on ΔΔQTcF was identified with an estimated population intercept of −2.96 ms (90 % CI −4.49 to −1.43 ms; $P = 0.0016$) and a negative slope of −0.0045 (90 % CI −4.49 to −1.43) ms per ng/mL, respectively. The safety profile after a single dose of lenvatinib was acceptable, with adverse events (AEs) of mild-to-moderate severity and no serious AEs.
Conclusions Lenvatinib had no clinically relevant effect on the QTc interval. Concentration-effect modeling supports the lack of QTc prolongation at high plasma concentrations.

Keywords QT · Thorough QT study · Oncology · Arrhythmia · Healthy volunteers

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Introduction

Angiogenesis is a prerequisite for tumor growth and metastasis and is therefore a target for antitumor drug development. Lenvatinib (previously E7080) is an oral once-daily dosed multityrosine kinase inhibitor (TKI) of vascular endothelial growth factor (VEGF) receptor 1–3, fibroblast growth factor receptor 1–4, platelet-derived growth factor receptor α, RET (rearranged during transformation), and KIT [1, 2].

In preclinical studies, lenvatinib inhibited VEGF-driven human umbilical vein endothelial cell proliferation and tube formation, and significantly inhibited the tumor growth of human lung (H460) and colorectal (Colo205) mouse xenograft models in vivo at doses of 1–100 mg/kg, prompting clinical investigation of lenvatinib as an anticancer agent [2].

A phase I dose-escalation study in patients with advanced solid tumors showed that lenvatinib had an acceptable

toxicity profile and preliminary activity for durable disease control [3]. A phase I study showed that lenvatinib administered once daily has a predictable absorption and elimination profile [4]. Lenvatinib had acceptable toxicity at doses up to 25 mg/day and encouraging antitumor activity in patients with melanoma and renal cell carcinoma.

A number of previously marketed noncardiovascular drugs, most notably terfenadine (an antihistamine) and cisapride (a gastrointestinal prokinetic agent), caused ventricular proarrhythmias, so-called torsades de pointes, a potentially life-threatening arrhythmia caused by delayed cardiac repolarization, which can be observed as surface electrocardiogram (ECG) QT prolongation [5–7]. The International Conference on Harmonisation subsequently issued a guidance [8] recommending all systemically available drugs be tested during clinical development for their proclivity to cause QT prolongation. Central to the guidance is the "thorough QT/QTc (TQT) study" in healthy volunteers, which evaluates the effect on TQT of the investigational compound, a placebo, and a positive control, i.e., a drug that causes TQT prolongation. Tested doses of the investigational drug need to generate plasma levels well in excess of those expected in patients. In most cases, this means that a supratherapeutic dose of the investigational drug needs to be administered.

In oncology, exposing healthy volunteers to investigational drugs is often not feasible, as they are genotoxic. Instead, features from the TQT study are applied to the extent possible to studies in cancer patients [9]. Lenvatinib is not genotoxic; therefore, this TQT study followed the design in the E14 guidance [8]. A single dose of lenvatinib was administered to healthy volunteers, and concentration-effect modeling was used to project the QT effect at high plasma levels. The dose used, 32 mg, is 1.33 times the largest daily dose being studied clinically. In a previous study in patients with solid tumors, no accumulation between single and multiple dosing was observed [4], and thus, it was anticipated that 32 mg would produce plasma levels greater than those seen in patients.

Methods

Study design

The study was a randomized, placebo- and positive-controlled, single-dose, 3-period, crossover, TQT study. Healthy male and female volunteers above 18 years of age were eligible to participate. Subjects with any clinically significant abnormality, including a QTc interval of >450 ms, a history of myocardial infarction, syncope, cardiac arrhythmias, hypertension, a history of unstable heart disease or additional risk factors for torsades de pointes, including heart failure, hypokalemia, or a family history of congenital long QT syndrome, or unexplained cardiac arrest were excluded.

Subjects were randomized in an equal ratio to 1 of 6 possible treatment sequences (BAC, BCA, ACB, ABC, CBA, or CAB). The study treatments were single doses of the following:

Treatment A: Lenvatinib (32 mg)
Treatment B: Moxifloxacin (Avelox® 400 mg)
Treatment C: Placebo

The appearance of the placebo capsules was identical to the lenvatinib capsules. Moxifloxacin was administered open label. During a full baseline day before treatment period 1, all subjects received placebo. On this day, a continuous ECG recording was performed with the objective to obtain a sufficiently broad range of heart rates (HRs) for the calculation of an individualized HR-corrected QTc in case lenvatinib would cause a significant HR effect [10].

On the first day of each 14-day period, subjects took the assigned study drug in the morning and remained in the clinic unit for 24 h. Subjects fasted from at least 8 h prior to until 4 h postdosing and were then served meals standardized to content and timing. Water was available ad libitum except for 2 h before and after study drug administration.

The study was conducted at a single site and adhered to Good Clinical Practice guidelines as required by the applicable regulatory guidance and the World Medical Association Declaration of Helsinki, 2008. The protocol was approved by the site's institutional review boards (Alpha IRB and Alpha Independent Review Board, both of San Clemente, CA, USA), and all subjects provided written informed consent prior to participation.

ECG assessments

A 25-h continuous, high-resolution (1,000 Hz), 12-lead ECG was recorded on the day of dosing using a Mortara Surveyor Telemetry system (Mortara Instrument, Inc., Milwaukee, WI, USA) and stored on digital media. ECGs were extracted from the continuous recordings at prespecified time points (30, 20, and 10 min before dosing and 1, 2, 3, 4, 5, 6, 12, and 24 h postdose). Subjects were supine for at least 10 min prior to and 10 min after these time points in an undisturbed environment. The digital files were transferred to the central ECG laboratory (iCardiac Technologies, Inc., Rochester, NY, USA) for processing. The staff at iCardiac was blinded to all treatments. ECGs were extracted from the continuous recordings using the TQT-Plus® software (iCardiac Technologies, Inc.), which facilitates extraction of ECG strips from periods of stable HR and high signal-to-noise ratio. Ten 10-second ECG tracings

were extracted from the 5-min window that preceded each assessment. Interval measurements were performed using COMPAS, a software package developed at the University of Rochester Medical Center, Rochester, NY, USA [11], in all recorded beats in the ten replicates. Beats were analyzed and deemed "high confidence" versus "low confidence." All low-confidence beats were reviewed manually for Q and T offset placements and adjudicated using pass–fail criteria. If measurements were deemed incorrect, no manual adjustments were made and the values from these beats were not used in the analysis. The overall quality control process was overseen by iCardiac's Chief Medical Officer. All high-confidence beats and low-confidence beats found acceptable by manual review were included in the analysis of QT, RR, and QTcF. The PR and QRS intervals were measured using a semiautomated technique on 3 of the 10 ECG tracings with the highest quality; T-wave morphology was assessed fully manually (visually).

Statistical analysis

The safety analysis set included all subjects who received at least one dose of study drug and had at least one postdose safety assessment. The pharmacokinetic (PK) analysis set included all subjects who received at least one dose of study drug and had sufficient PK data to derive at least one PK parameter. The pharmacodynamic analysis set included subjects who received study drug as scheduled and had analyzable ECG data for at least one treatment period. All statistical analyses were performed using SAS software, version 9.1.3 (SAS Institute, Inc., Cary, NC, USA), with the exception of the analyses for the concentration-effect modeling, which were performed using the statistical software R for Windows system (version 2.11.1).

Analyses related to ECG assessment

The primary end point was the baseline-adjusted, placebo-corrected effect on QTcF (ΔΔQTcF), and the secondary end points included HR, PR, QRS, QTcB, T-wave morphology changes, and the relationship between lenvatinib plasma concentrations and ΔΔQTcF interval. The statistical assessment of the QTcF effect was based on the 90 % two-sided confidence interval (CI) for the time-matched mean difference in change-from-baseline QTcF between lenvatinib and placebo using a mixed-effects model. This model included fitting terms for sequence, period, treatment, time, and time-by-treatment interaction as fixed effects, baseline QTc as a covariate, and subject nested within sequence as a random effect. The change-from-baseline at each time point (ΔQTcF) was used as the dependent variable. For this analysis, the least squares mean and 90 % two-sided CI at each time point were calculated within the model for the contrasts "lenvatinib–placebo" and "moxifloxacin–placebo." A negative study was concluded if the upper bound (UB) of the two-sided 90 % CI of the baseline-adjusted, placebo-corrected QTcF for lenvatinib at all time points was below 10 ms. Assay sensitivity was assessed by comparing the one-sided 95 % lower confidence boundary using the above model on the time-matched mean difference in change–from-baseline QTcF between moxifloxacin and placebo. If the lower confidence boundary was more than 5 ms for any of the predefined time points, 1, 2, 3, and 4 h postmoxifloxacin administration, assay sensitivity was confirmed [12]. The Hochberg procedure [13] was used for adjustment for multiplicity. The mixed-effects model used to analyze QTcF was also repeated for other ECG parameters (i.e., HR, PR, QRS, and QTcB).

The analysis results for categorical outliers and T-wave morphology were summarized by treatment in frequency tables with counts and percentages for both number of subjects and number of time points. For categorical outliers, the number (percentage) of subjects and time points with QTc above 450, 480, and 500 ms, and ΔQTc exceeding 30 and 60 ms was conducted. For T-wave morphology, the analysis was focused on change-from-baseline, i.e., treatment-emergent changes.

A sample size of 48 evaluable subjects was predicted to provide at least 90 % power to demonstrate that the UB of the two-sided 90 % CI of the time-matched mean effect of lenvatinib on QTcF was <10 ms for all postdosing time points, assuming a true mean difference of 5 ms and a within-subject standard deviation (SD) of ΔQTcF of 8 ms.

The relationship between ΔΔQTcF and lenvatinib concentrations was investigated by a linear mixed-effects modeling approach:

$$\Delta\Delta\mathrm{QTcF}_{ij} = \mathrm{Intercept}_i + \mathrm{Slope}_i \cdot \mathrm{Conc}_{ij} + \varepsilon_{ij}$$

where $\Delta\Delta\mathrm{QTcF}_{ij}$ was the time-matched, placebo-corrected, change-from-baseline QTcF for subject i at time j with lenvatinib concentration Conc_{ij}. The residual ε_{ij} was assumed to be identical, independent, normally distributed with a mean of 0, and a variance of σ^2.

The following three linear models were considered: (1) a linear model with an intercept, (2) a linear model with mean intercept fixed to 0 (with variability), and (3) a linear model with no intercept. Time-matched concentration was included in the model as a covariate, and subjects were included as a random effect for both intercept and slope, when applicable [14, 15].

The model that fit the data best was used for predicting mean ΔΔQTcF and its corresponding 90 % two-sided CI at the geometric mean maximum plasma concentration of lenvatinib ($C_{\max}$). The adequacy of the selected best model was assessed by the lowest Akaike information criterion (AIC) and goodness-of-fit plots. This plot was used

to check the assumption of linearity between lenvatinib concentrations and ΔΔQTcF, and how well the predicted ΔΔQTcF matched the observed data in the regions of interest. The goodness-of-fit plot was generated by binning the independent variable (i.e., concentrations) into deciles. The observed mean ΔΔQTcF with 90 % CI within each decile was computed and plotted at the corresponding median concentration within the decile. The decile ranges were added in the bottom of the graphs to illustrate the span of each decile and possible skewness of the tails.

For each time point, the SD of the observed ΔQTcF was calculated across all subjects, separately for placebo, moxifloxacin, and lenvatinib. The mean SD over all time points was thereafter calculated.

Pharmacokinetic analysis

To fully characterize the plasma concentration versus time curve, blood samples were obtained prior to and then 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, and 96 h after the dose in each treatment period. Plasma lenvatinib and moxifloxacin concentrations were then quantified by liquid chromatography/mass spectrometry/mass spectrometry using validated methods. Maximum concentration (C_{max}), total exposure [area under the curve AUC_{0-t}, AUC_{0-inf}], time from dose administration to maximum concentration (t_{max}), and terminal elimination half-life were estimated using noncompartmental analysis. Lenvatinib plasma concentrations and PK metrics were summarized using descriptive statistics.

Safety analyses

Safety evaluations included monitoring of AEs and serious AEs, clinical laboratory assessments (hematology, clinical chemistry, and urine values), vital sign measurements, 12-lead ECG results, and physical examination findings.

Results

Patient disposition and baseline characteristics

A total of 52 subjects were randomized, and 50 subjects completed the study. Two subjects withdrew consent prior to completion. Fifty-two, 51, and 51 subjects were included in the safety, PK, and pharmacodynamic data sets, respectively. In the safety analysis set, 54 % of the subjects were male, 60 % were White, 25 % were Black, and 15 % were of other races, including 2 % Hawaiian or other Pacific Islanders. The mean age of subjects was 34 (SD = 13.8) years, and their mean body mass was 83 (21.0) kg. Predose baseline ECG parameters were comparable across treatment arms.

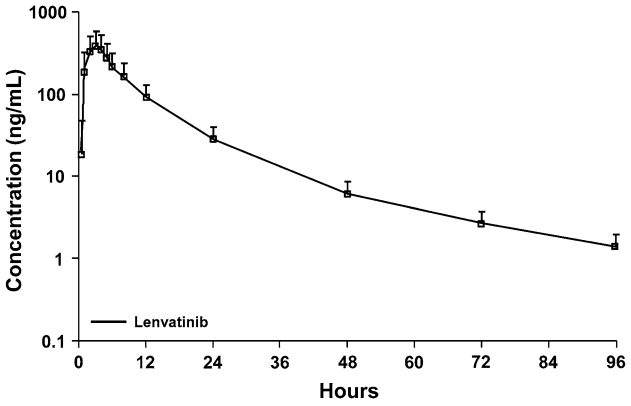

Fig. 1 Semilog plot of mean (+SD) lenvatinib plasma concentration versus nominal time

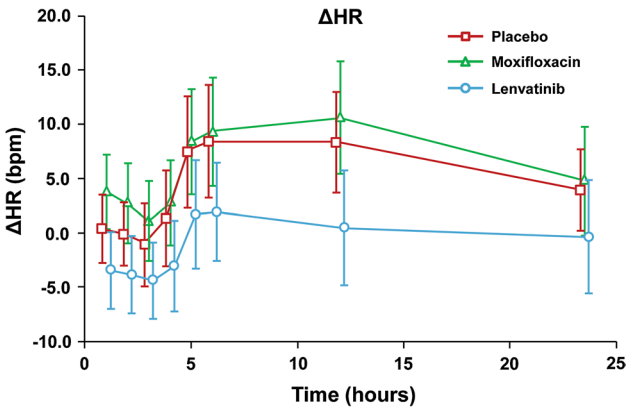

Fig. 2 Change-from-baseline heart rate (Δ*HR*; mean ± SD) across postdosing time points

Lenvatinib plasma concentration

Lenvatinib plasma concentrations versus nominal times are presented in Fig. 1. The peak plasma level (arithmetic mean ± SD) of 417 ± 201.8 ng/mL was observed at a median of 3.0 h (range 1.5–5.0) after dosing; AUC_{0-t} was 3,614.1 ± 1,420.3 ng/mL h, and the median half-life was 21.3 h (range 6.6–30.9). Mean peak plasma levels of moxifloxacin reached 3.2 μg/mL and were observed at a median of 2.0 h after dosing.

Effect on heart rate

The treatment effect on HR is shown in Fig. 2. The change-from-baseline HR (ΔHR) in the placebo and moxifloxacin treatment arms was similar and followed the same diurnal pattern with an increase in the HR after the first 4 h. The same diurnal pattern of ΔHR was also observed after administering lenvatinib, but the overall level of ΔHR was

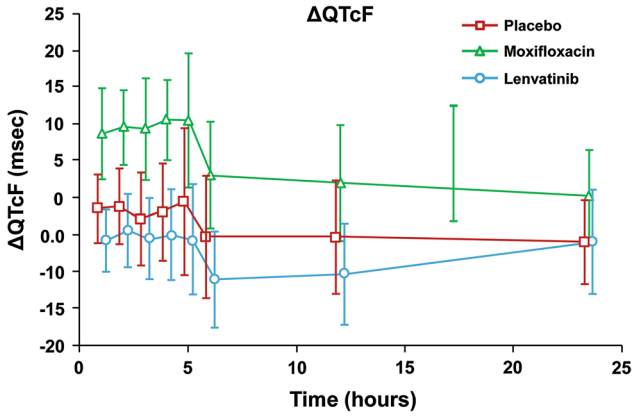

Fig. 3 Change-from-baseline QTcF (Δ*QTcF*; mean ± SD) across postdosing time points

lower with an initial reduction that reached 5 bpm. The mean placebo-corrected ΔHR (ΔΔHR) on lenvatinib treatment was lowered by 3–5 bpm during the first 4 h and by 6 (90 % CI 4.7–7.6) bpm, 7 (90 % CI 5.2–8.1) bpm, and 8 (90 % CI 6.6–9.6) bpm at 5, 6, and 12 h postdosing.

Effect on cardiac repolarization: QT interval and T-wave morphology

Moxifloxacin increased the mean ΔQTcF during the first 5 h postdosing with a peak effect at 4 and 5 h of 10.6 and 10.5 ms, respectively (Fig. 3). During placebo treatment, ΔQTcF remained unchanged during the first 5 h and was then slightly reduced to around −5 ms. The same pattern as on placebo was observed following lenvatinib although slightly more pronounced. At 6 h, the ΔQTcF reached −11.1 ms. Consequently, a small ΔΔQTc shortening was observed after dosing of lenvatinib and ΔΔQTc prolongation exceeding 10 ms could be confidently excluded (Table 1). The mean ΔΔQTcF never exceeded 0.07 ms nor did the UB of the 90 % CI exceed 2 ms. The sensitivity of the study [12] was confirmed by the ΔΔQTcF response after a single dose of moxifloxacin 400 mg. The mean peak effect reached 12.6 ms (at 4 h) and the lower bound of the 90 % CI exceeded 5 ms at all four prespecified time points (Table 1).

The QTcF interval exceeded 450 ms in five subjects during treatment with moxifloxacin and in no subjects during treatment with placebo or lenvatinib. There were no subjects on any treatment that had a ΔQTcF value exceeding 30 ms.

The mean SD of the observed ΔQTcF across time points on placebo and moxifloxacin was 6.2 ms and on lenvatinib 5.9 ms.

One subject exhibited flat T-waves at baseline and during placebo treatment. This subject also exhibited a notched T-wave during placebo treatment. No T-wave morphology changes or abnormal U-waves were noted on treatment with moxifloxacin or lenvatinib.

Effect on PR and QRS intervals

Overall, PR interval changes were very small in all treatment arms, and all ΔPR values were within −10 to 4 ms (Fig. 4, Panel a). The largest mean placebo-corrected ΔPR (ΔΔPR) on-treatment with lenvatinib reached 8.5 ms (90 % CI 6.0–10.9) at 5 h. The PR interval exceeded

Table 1 Time-matched ΔQTcF across treatments and time points

Treatment	Time postdose (h)	LS mean		90 % CI for LS means difference		
		Treatment (ms)	Placebo (ms)	LS mean difference (treatment–placebo)	Lower (ms)	Upper (ms)
Lenvatinib 32 mg	1	−5.93	−1.58	−4.35	−6.02	−2.68
	2	−4.48	−1.17	−3.31	−4.86	−1.76
	3	−5.68	−2.76	−2.92	−4.90	−0.94
	4	−5.14	−1.93	−3.20	−5.04	−1.36
	5	−5.76	−0.56	−5.20	−7.75	−2.65
	6	−11.06	−5.33	−5.72	−7.76	−3.69
	12	−10.47	−5.34	−5.13	−7.20	−3.06
	23.5	−5.96	−6.03	0.07	−1.76	1.90
Moxifloxacin 400 mg[a]	1	8.79	−1.58	10.37	8.68	12.06
	2	9.69	−1.17	10.86	8.74	12.99
	3	9.46	−2.76	12.22	9.85	14.58
	4	10.70	−1.93	12.63	10.24	15.02

Δ*QTcF* change-from-baseline QTcF, *CI* confidence interval, *h* hours, *LS* least squares, *msec* milliseconds

[a] Hochberg procedure was used for correction of multiplicity to calculate the confidence limits

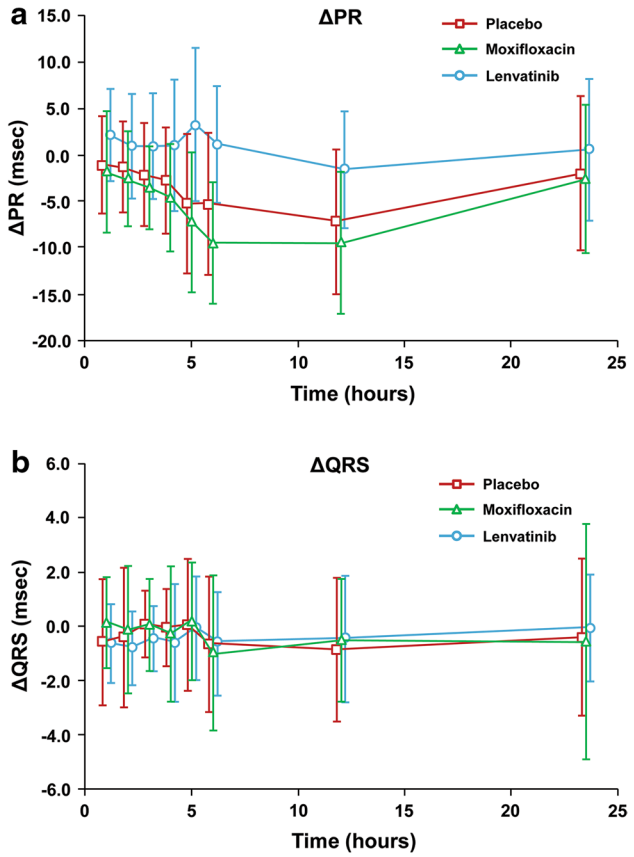

Fig. 4 **a** Change-from-baseline PR (Δ*PR*; mean ± SD) across postdosing time points. **b** Change-from-baseline QRS (Δ*QRS*; mean ± SD) across postdosing time points

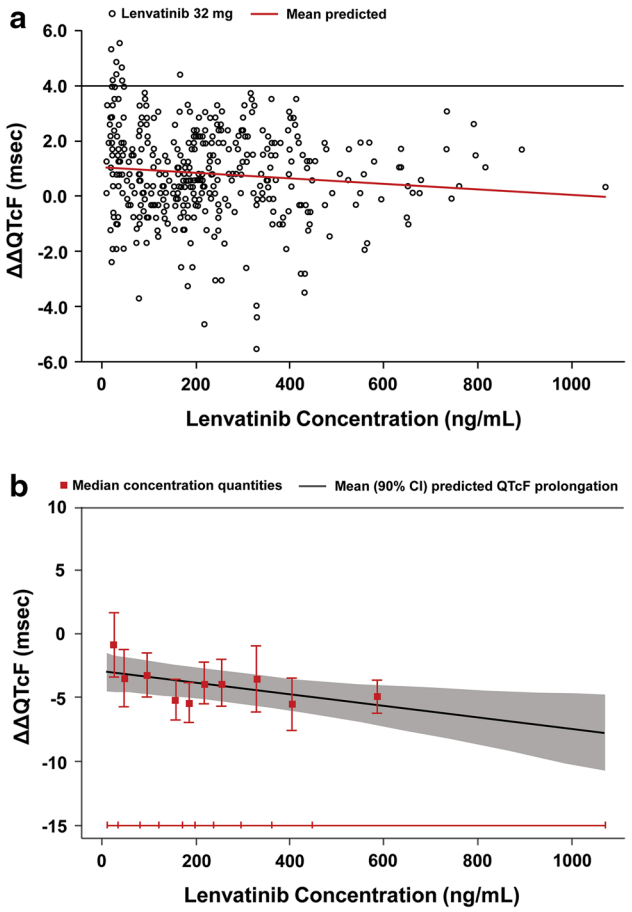

Fig. 5 **a** Observed lenvatinib plasma concentration/ΔΔQTcF data with population mean predictions (*solid red line*). **b** Goodness-of-fit plot for observed and predicted relation between lenvatinib plasma levels and ΔΔQTcF. *Red vertical bars* denote the observed mean ΔΔQTcF with 90 % CI within each plasma concentration decile. The *solid black line* with *gray-shaded area* denotes the model-predicted mean ΔΔQTcF with 90 % CI. The *horizontal red line* with notches shows the range of plasma concentrations within each decile. *CI* confidence interval

200 ms at any time point postdosing in one subject receiving placebo and in one subject receiving lenvatinib.

Treatment with lenvatinib did not have any effect on the QRS interval (Fig. 4, Panel b). The mean placebo-corrected change-from-baseline QRS did not exceed ±0.6 ms. The QRS interval exceeded 120 ms at least at one time point postdosing in three subjects on placebo, two on moxifloxacin, and three on lenvatinib.

Concentration-effect modeling

The linear model with an intercept fit the data best among the three candidate models using several criteria, including the smallest AIC and by visual review of diagnostic plots. The relationship between the individually observed lenvatinib concentrations and associated ΔΔQTcF is visualized in Fig. 5, Panel a. The goodness-of-fit plot (Fig. 5, Panel b) shows the observed mean ΔΔQTcF (90 % CI) within each lenvatinib plasma concentration decile and the model-predicted mean ΔΔQTcF with its 90 % CI. A concentration-dependent effect of lenvatinib on ΔΔQTcF was identified with an estimated population intercept of −2.96 ms (90 % CI −4.49 to −1.43 ms) and a negative slope of −0.0045 (90 % CI −4.49 to −1.43) ms per ng/mL, respectively. The mean C_{max} of lenvatinib following administration of 32 mg was 417 ng/mL (SD = 201.8). Using the concentration-effect model, ΔΔQTcF is projected to −4.83 ms (90 % CI −6.12 to −3.53 ms) at this plasma level.

Safety and tolerability

The incidence of treatment-emergent AEs (TEAEs) across treatment groups was similar. There was a slightly higher incidence of treatment-related TEAEs in the lenvatinib group than the other two treatment groups. Of the 52 subjects randomized, 14 (28 %) subjects who received moxifloxacin reported TEAEs, nine (18 %) of which were

considered treatment-related. Thirteen (25.5 %) subjects who received lenvatinib 32 mg experienced TEAEs, and 11 (21.6 %) were considered treatment-related. Twelve (24 %) subjects experienced at least one TEAE in the placebo group and five (10 %) were considered treatment-related. The most frequently reported TEAE (>5 %) across treatment groups was headache. Other frequently reported events were diarrhea, paresthesia, nausea, fatigue, dysmenorrhea, and oropharyngeal pain. None of the treatment-related AEs were regarded as severe or serious in nature, or resulted in death.

Discussion

Definitive clinical QT assessments with oncology drugs are often performed in cancer patients rather than in healthy volunteers, due to safety concerns. Moreover, the use of placebo and moxifloxacin as a positive control can be difficult to ethically justify. Many studies with oncology agents are therefore uncontrolled [16]. Many of these studies are not formally powered to exclude a QTc effect at the same threshold of concern as for others agents, i.e., 10 ms [17]. The general principle for studies performed in cancer patients has therefore been to incorporate as many elements as feasible from the TQT study design [9].

Previous studies intended to obtain definitive assessment of the effect on the QTc interval with TKIs have been performed both in cancer patients and in healthy volunteers. Tasocitinib was evaluated in a TQT study in 60 healthy volunteers with a single supratherapeutic dose of 100 mg, placebo, and moxifloxacin. The 100-mg dose was estimated to generate 3.5-fold higher plasma levels as those observed in patients on a therapeutic dose. The study was clearly negative, and a QTcF effect above 10 ms could be excluded at all postdosing time points with an essentially flat relationship between plasma levels and QTcF [18]. Bosutinib was also tested in 60 healthy volunteers in a 2-part, single-dose, crossover, placebo- and moxifloxacin-controlled study [19]. In a separate part of the study, supratherapeutic bosutinib plasma levels were obtained with concomitant dosing of bosutinib 500 mg (the therapeutic dose) and a strong CYP P450 3A4 (CYP3A4) inhibitor, ketoconazole. Since ketoconazole has a QTc effect in itself [20], the effect of bosutinib in this part was adjusted for ketoconazole. The UBs of the 90 % CI were below 10 ms at all time points postdosing for both the therapeutic and the supratherapeutic bosutinib dose; the largest observed effect on the population-specific QT correction (ΔΔQTcN) was 4.5 ms (UB of 90 % CI 6.8 ms) at 8 h. A slightly positive relationship between bosutinib plasma levels and ΔQTcN was shown. Other TKIs have been tested in cancer patients. Sunitinib was evaluated in 24 patients with solid tumors [17]. Consistent with nonclinical assays that had demonstrated a "QT-signal," sunitinib prolonged QTcF with a largest ΔQTcF of 5.6 ms (UB of 90 % CI 9.3 ms) at steady-state/therapeutic plasma levels and 15.4 ms (UB of 90 % CI 22.4 ms) at supratherapeutic concentrations on day 9. The ΔQTcF correlated with sunitinib exposure. Sorafenib was tested in 31 patients with advanced cancer in an uncontrolled, open-label study with a therapeutic dose of 400 mg twice daily [21]. Somewhat unusual, the primary end point was the QTc effect at each subject's t_{max} at steady state (Day 1 of Cycle 2); a QTc effect of 9.0 ms (SD = 18 ms) was observed using this approach, whereas the time-matched effect ranged between 4.2 and 5.8 ms.

Lenvatinib is currently under clinical investigation for treatment of radioiodine-refractory differentiated thyroid cancer in a phase III trial, in addition to phase I and phase II studies in hepatocellular carcinoma, renal cell carcinoma, and nonsmall cell lung carcinoma. Preclinical studies of lenvatinib have not demonstrated a signal for QT prolongation, including no effect on the human ether-a-go-go-related gene (hERG) potassium current in vitro and no ECG changes or QTc prolongation in dogs (Eisai Product Creation Systems, data on file). In this TQT study, a single dose of lenvatinib was given to healthy volunteers, which could be justified based on previously demonstrated low toxicity and an acceptable side effect profile (Eisai, data on file), to evaluate the drug's effect on ECG parameters. The selected dose of 32 mg, the highest dose that has been administered to humans, is somewhat higher than the highest therapeutic dose of 24 mg. Since there is no accumulation of the drug between single and multiple dosing [4], and there is no food effect [22], 32 mg was estimated to generate supratherapeutic plasma levels. Also, drug–drug interactions following coadministration of other drugs are not expected to increase lenvatinib exposure to levels higher than those seen in this study. Lenvatinib is extensively metabolized prior to elimination [23]. However, systemic exposure to lenvatinib insignificantly increases with coadministration of ketoconazole, a strong CYP3A4 inhibitor (geometric least squares mean ratios of AUCs increased 14 % with the bounds of the CIs within the generally accepted bioequivalence limits) [24, 25].

Lenvatinib did not cause a clinically meaningful effect on the QTc interval and demonstrated a small observed QTc shortening at most postdosing time points. An effect on ΔΔQTcF exceeding 10 ms could be confidently excluded; in fact, the UB of the 90 % CI did not exceed 2 ms at any time point (Table 1). Lenvatinib had a mild HR lowering effect of around 5–7 bpm during the first 6 h postdosing. The use of a fixed algorithm for HR correction of the QT interval, such as QTcF, or a correction derived from a narrow range of HRs, such as QTcI from time points at rest only, has been criticized when pronounced

HR changes are observed. However, an HR effect at this level is within the range in which it is regarded as appropriate to use QTcF [26]. The study's ability to detect a small QTc change was confirmed by the QTc effect after dosing of a single 400-mg dose of moxifloxacin: The mean peak effect reached 12.6 ms at 4 h and the lower bound of the 90 % CI exceeded 5 ms at all four prespecified time points (Table 1). The precision of the QTc measurements—which incorporates all elements that can influence the variability of the measurements (experimental conditions at the site, appropriateness of HR correction, and measurements technique)—measured as the observed mean SD of ΔQTcF across time points, was 6.2 ms on placebo and 5.9 ms on lenvatinib. This level of precision compares favorably with other studies in healthy volunteers [27] and is difficult to achieve in studies in cancer patients. The effect of lenvatinib on cardiac conduction was small; the largest on-treatment mean ΔΔPR was 8.5 ms (90 % CI 6.0–10.9), observed 5 h after dosing. An effect on the PR interval at this level is likely of low clinical relevance in an oncology population. No effect was seen on the QRS interval.

Observed median plasma levels after dosing of lenvatinib 32 mg in this study were lower than anticipated and did not reach the anticipated 1.33-fold margin versus therapeutic plasma levels expected in patients receiving 24 mg. In patients with solid tumors, after 4 weeks of treatment (25 mg, once daily), the median concentration of lenvatinib was 579.1 ng/mL (range 314.9–705.7) [4]; in contrast, the observed median C_{max} in this study was 395 ng/mL (range 182–1,070). It should, however, be noted that the C_{max} range observed in the current study encompassed the range previously observed in patients; moreover, the previous study in patients with solid tumors utilized an earlier tablet formulation with about 14 % greater bioavailability [28], whereas the ongoing phase III registration studies use the same capsule as in this TQT study.

It can therefore be expected that the plasma levels observed in this study will cover those seen in patients in the targeted indication. A negative relationship between lenvatinib plasma levels and the model-predicted ΔΔQTcF was observed with a slope of −0.0045 (90 % CI −4.49 to −1.43) ms per ng/mL, which corresponds to a small QT shortening effect. Using the concentration-effect model, ΔΔQTcF is projected to −4.83 ms (90 % CI −6.12 to −3.53 ms) at 417 ng/mL (SD = 201.8), the observed mean peak plasma level. Importantly, it is also apparent that an effect exceeding 10 ms can be excluded within the tenth decile of observed plasma levels. In this decile, the plasma concentrations ranged from 446 to 1,070 ng/mL with a median of 586 ng/mL. As noted above, these concentrations mirror maximum steady-state plasma concentrations observed in patients. In this decile, the mean ΔΔQTcF was −4.88 ms (90 % CI −6.20 to −3.55). This supports the assertion that lenvatinib does not cause QTc prolongation at clinically relevant, high plasma levels.

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Conflict of interest B Darpo: consultant to Eisai Product Creation Systems and iCardiac Technologies, Inc.; stock holdings of iCardiac. M Zhou: employee of iCardiac Technologies, Inc. RC Shumaker, J Fan, M Ren, G Martinez, J Aluri: employees of Eisai Product Creation Systems.

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