Abstract CT128

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Effect of Futibatinib on QT/QTc Interval: a Randomized, Controlled, Double-Blind Study

Ikuo Yamamiya,[1] John Laabs,[2] Daryl Sonnichsen,[3] Mark Mina,[1] Yaohua He,[1] Karim Benhadji[1]

[1]Taiho Oncology, Inc., Princeton, NJ; [2]Celerion, Tempe, AZ; [3]Sonnichsen Pharmaceutical Associates, LLC, Collegeville, PA

Background

- Futibatinib is an oral, highly selective, irreversible FGFR1–4 inhibitor[1]
- Futibatinib demonstrated tolerability and clinical activity in patients with advanced tumors harboring *FGFR* aberrations in a phase 1 dose escalation/expansion study[2,3]
  - Futibatinib 20 mg once daily was established as the recommended phase 2 dose, based on pharmacokinetic (PK), pharmacodynamic, and safety data[2]
  - PK analysis has demonstrated no significant accumulation of futibatinib exposure after multiple doses and no significant circulating metabolites in plasma[2,4]
- To assess the cardiac safety of futibatinib, a thorough QT study[5] was conducted to evaluate the effect of futibatinib on the heart rate–corrected QT (QTc) interval

Methods

- This was a phase 1, randomized, active-controlled, single-dose, 4-period crossover thorough QT study that enrolled healthy nonsmokers aged 18–55 years
- On day 1 of each of the 4 treatment periods, participants received a single dose of 1 of the following:
  - **Futibatinib, therapeutic dose** (double-blind): 20 mg (5 × 4-mg tablets) and futibatinib-matching placebo (15 × placebo tablets)
  - **Futibatinib, supratherapeutic dose** (double-blind): 80 mg (20 × 4-mg tablets)
  - Placebo control (double-blind): futibatinib-matching placebo (20 × placebo tablets)
  - Moxifloxacin (positive QTc-prolongation control; open label): 400 mg (1 × 400-mg tablet)
- The sequence of the 4 treatments was randomized; ≥7 days were allowed between administration of each treatment
- The primary endpoint was the difference in change from baseline in QTcF (QT interval corrected using Fridericia's formula) between futibatinib and placebo (ddQTcF) at the time points tested
- Secondary endpoints included placebo-corrected change from baseline in other electrocardiogram (ECG) parameters, PK, and safety
- In each period, cardiodynamic ECGs were performed and PK blood samples were collected before and at various time points through 24 h after dosing; PK samples were also collected 48 h after futibatinib and placebo dosing
- Safety was monitored throughout the study period

Results

Participants

- A total of 48 participants (28 male and 20 female) were enrolled and randomized to 1 of 12 treatment sequences
  - 44 completed the study, and 4 discontinued early
  - All 48 participants received ≥1 dose of futibatinib, were evaluable for futibatinib PK, and were included in the analysis populations
- The mean age was 38.6 years (range, 20–55), mean body weight was 77 kg (range, 52–106), and mean body mass index was 27.3 kg/m^2 (range, 19.5–32.0)

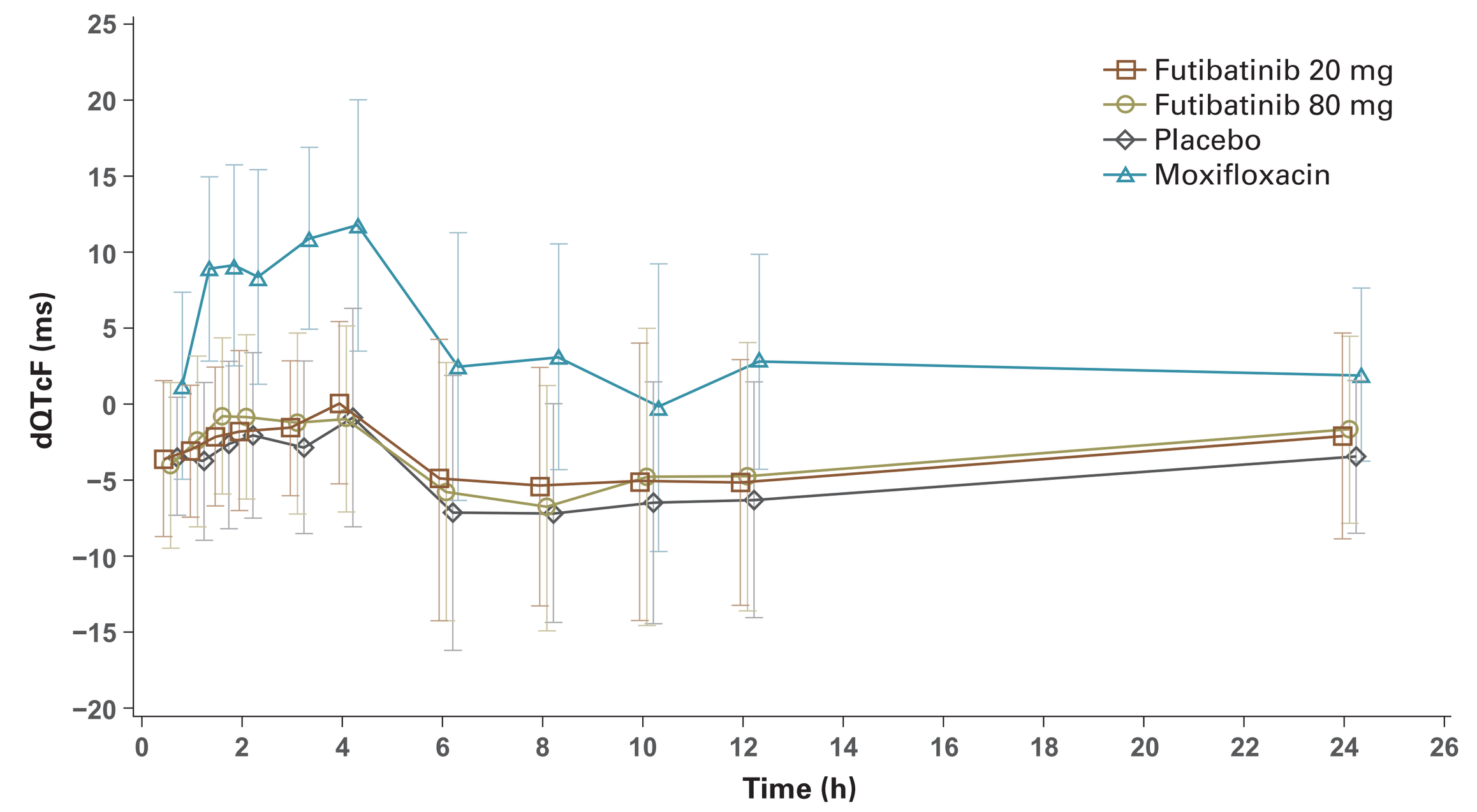
Cardiodynamics

- Mean QTcF change from baseline (dQTcF) over time after dosing is shown in **Figure 1**
- The ddQTcF ranged from 0.13 to 2.47 ms with 20 mg futibatinib and from –0.04 to 2.46 ms with 80 mg futibatinib from 0.5 to 24 h after dosing (**Table 1**)
  - Upper limits of the 2-sided 90% confidence intervals (CIs) of these values remained well below 10 ms (the threshold of clinical concern) at all time points, indicating that futibatinib did not prolong the QTc interval
- Lower limits of the 2-sided 97.5% CIs of the difference in dQTcF between moxifloxacin and placebo exceeded 5 ms (range, 8.06–11.43) at the time points analyzed, which demonstrated assay sensitivity (**Table 2**)
- No clinically significant effects of futibatinib on heart rate, other ECG parameters (eg, PR, QRS, or QT intervals), or ECG morphology were identified (data not shown)
- Exposure–response modeling indicated no significant relationship between plasma futibatinib concentration and the ddQTcF (slope, 0.0000; 90% CI, –0.0021 to 0.0021; *P*=0.973; **Figure 2**)

PK

- Exposure to futibatinib increased in a dose-dependent manner between the 20-mg and 80-mg doses (**Table 3** and **Figure 3**)
  - The futibatinib area under the concentration curve from time 0 to infinity (AUC_{0-inf}) and maximum plasma concentration (C_{max}) increased by 4.5- and 3.3-fold, respectively
- The C_{max} values observed with 80 mg futibatinib (median, 553 ng/mL; range, 71–1160) exceeded any C_{max} observed or expected with the 20-mg daily therapeutic dose (median, 199 ng/mL; range, 33–321) at steady state

Figure 1. Mean (SD) dQTcF over time by treatment



dQTcF, change from baseline in QT interval corrected using Fridericia's formula; SD, standard deviation.

Table 1. ddQTcF

Time (h)[a]	Placebo dQTcF,[b] ms	Futibatinib 20 mg dQTcF,[b] ms	Futibatinib 20 mg Difference, ms (90% CI)[c]	Futibatinib 80 mg dQTcF,[b] ms	Futibatinib 80 mg Difference, ms (90% CI)[c]
0.5	–3.83	–3.70	0.13 (–1.93 to 2.18)	–3.87	–0.04 (–2.07 to 2.00)
1.0	–4.12	–3.18	0.94 (–1.12 to 3.00)	–2.30	1.82 (–0.21 to 3.85)
1.5	–3.09	–2.26	0.83 (–1.23 to 2.89)	–0.64	2.46 (0.43 to 4.49)
2.0	–2.46	–1.88	0.58 (–1.48 to 2.63)	–0.71	1.75 (–0.28 to 3.78)
3.0	–3.25	–1.74	1.50 (–0.55 to 3.56)	–1.13	2.12 (0.09 to 4.15)
4.0	–1.25	–0.04	1.21 (–0.85 to 3.26)	–0.82	0.43 (–1.60 to 2.46)
6.0	–7.57	–5.10	2.47 (0.40 to 4.54)	–5.62	1.95 (–0.09 to 3.99)
8.0	–7.54	–5.52	2.01 (–0.04 to 4.07)	–6.66	0.88 (–1.15 to 2.91)
10.0	–6.85	–5.22	1.63 (–0.43 to 3.68)	–4.65	2.21 (0.17 to 4.24)
12.0	–6.73	–5.27	1.45 (–0.60 to 3.51)	–4.61	2.12 (0.09 to 4.15)
24.0	–3.80	–2.27	1.53 (–0.53 to 3.58)	–1.55	2.25 (0.22 to 4.28)

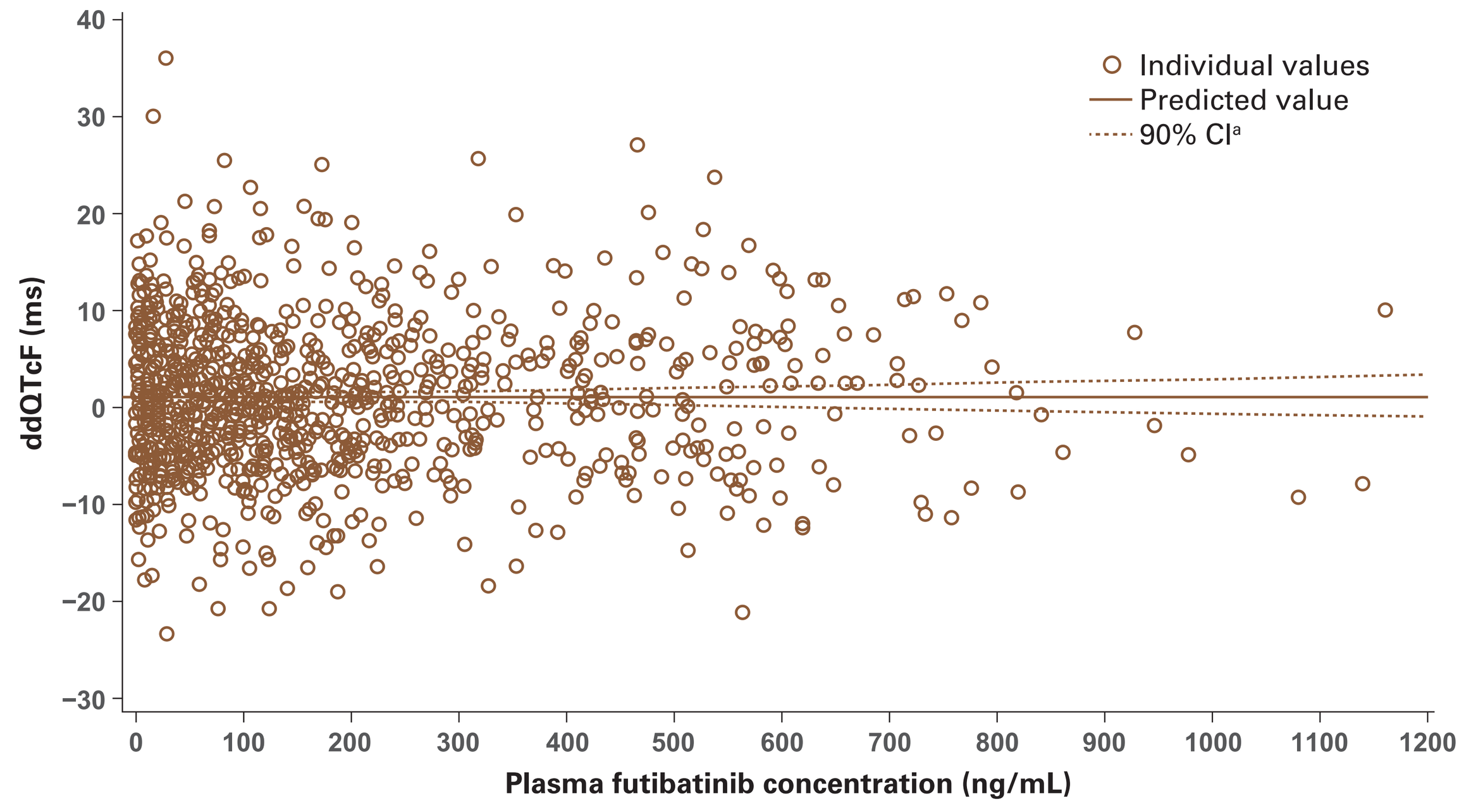
CI, confidence interval; dQTcF, change from baseline in QTcF (QT interval corrected using Fridericia's formula); ddQTcF, difference in dQTcF between futibatinib and placebo.
[a]After dosing. [b]Least-squares mean. [c]Futibatinib vs placebo; 2-sided 90% CI.

Table 2. Difference in dQTcF between moxifloxacin and placebo

Time (h)[a]	Placebo dQTcF,[b] ms	Moxifloxacin dQTcF,[b] ms	Difference, ms (97.5% CI)[c]
1.5	–3.09	9.13	12.22 (9.45–14.99)
2.0	–2.46	8.38	10.83 (8.06–13.60)
3.0	–3.25	10.95	14.19 (11.43–16.96)
4.0	–1.25	11.79	13.05 (10.28–15.82)

CI, confidence interval; dQTcF, change from baseline in QTcF (QT interval corrected using Fridericia's formula).
[a]After dosing. [b]Least-squares mean. [c]Moxifloxacin vs placebo; 2-sided 97.5% CI.

Figure 2. ddQTcF versus plasma futibatinib concentration



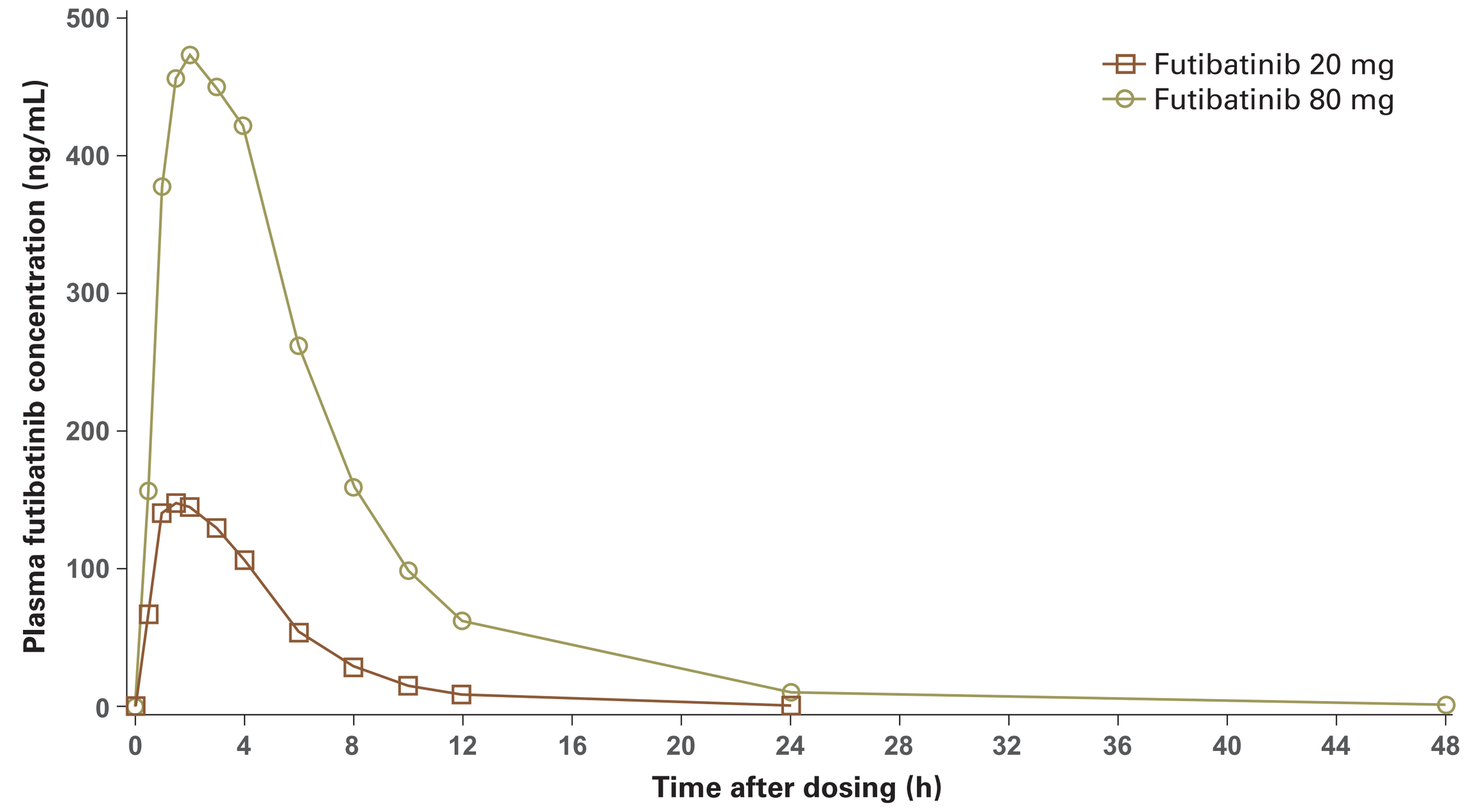
CI, confidence interval; ddQTcF, difference in change from baseline in QTcF (QT interval corrected using Fridericia's formula) between futibatinib and placebo.
[a]Exposure–response modeling was performed using the equation $dQTc_{i,k} = (\mu + Time_k + \eta_{\mu,i}) + \Theta_0(B_{QTc,i} - meanB) + (\Theta_1 + \eta_{c,i})C_{i,k} + \varepsilon_{i,k}$, where Θ_0 is the coefficient of baseline QTc, μ is the population mean, $Time_k$ is time after the dose (as a categorical factor), B is the individual baseline value, meanB is the mean baseline value, Θ1 is the slope of the concentration, η is multivariate normally distributed with mean 0 and variance Ω, and ε is normally distributed with a mean of 0 and variance of σ^2.

Table 3. Plasma futibatinib PK parameters

PK parameter	Statistic	Futibatinib 20 mg (n=45)[a]	Futibatinib 80 mg (n=47)[b]
AUC_{0-t}, ng·h/mL	Geometric mean (CV)	704.3 (68.7)	3206.0 (58.3)
AUC_{0-inf}, ng·h/mL	Geometric mean (CV)	713.5 (68.2)	3229.0 (57.6)
C_{max}, ng/mL	Geometric mean (CV)	165.2 (52.3)	541.5 (44.4)
	Median (range)	199 (33–321)	553 (71–1160)
T_{max}, h	Median (range)	1.538 (0.69–4.01)	2.001 (1.00–6.02)
$t_{1/2}$, h	Mean ± SD	2.23 ± 0.79	5.39 ± 2.28
CL/F, L/h	Mean ± SD	36.8 ± 45.2	31.1 ± 39.2
Vz/F, L	Mean ± SD	94.4 ± 57.6	219.0 ± 257.0

AUC_{0-t}, area under the plasma concentration–time curve from time 0 to the last quantifiable concentration; AUC_{0-inf}, area under the plasma concentration–time curve from time 0 to infinity; C_{max}, maximum plasma concentration; CL/F, total plasma clearance after oral administration; CV, coefficient of variation; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, terminal half-life; T_{max}, time to maximum plasma concentration; Vz/F, volume of distribution during the terminal elimination phase after oral administration.
[a]3 participants did not receive this treatment. [b]1 participant did not receive this treatment.

Figure 3. Mean plasma futibatinib concentration over time by dose



Safety

- Overall, 64 adverse events (AEs) were reported by 19 (40%) participants (**Table 4**)
- There were no deaths, serious AEs, or other significant AEs in this study

Table 4. Most common treatment-emergent AEs[a]

AE	All (N=48)	Futibatinib 20 mg (n=45)[b]	Futibatinib 80 mg (n=47)[c]	Placebo (n=47)[c]	Moxifloxacin (n=47)[c]
	Participants, n (%)				
Any	19 (40)	7 (16)	7 (15)	9 (19)	6 (13)
Headache	4 (8)	1 (2)	1 (2)	1 (2)	1 (2)
Oral herpes	3 (6)	1 (2)	1 (2)	0	1 (2)
Constipation	2 (4)	1 (2)	0	1 (2)	0
Cough	2 (4)	0	0	2 (4)	0
Nausea	2 (4)	0	0	1 (2)	1 (2)
Nodule	2 (4)	1 (2)	0	1 (2)	0
Papule	2 (4)	1 (2)	0	0	1 (2)
Rhinorrhea	2 (4)	0	1 (2)	2 (4)	0
Vomiting	2 (4)	0	1 (2)	0	1 (2)

AE, adverse event.
[a]Reported in ≥4% of all patients. [b]3 participants did not receive this treatment. [c]1 participant did not receive this treatment.

Conclusions

- A single therapeutic (20 mg) or supratherapeutic dose (80 mg) of futibatinib did not prolong the QTc interval or adversely affect other measures of heart function analyzed
  - The positive control, moxifloxacin 400 mg, prolonged the QTc interval substantially, demonstrating assay sensitivity
- Futibatinib exposure increased in a dose-dependent manner
- Administration of futibatinib was safe and well tolerated in healthy participants

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Contact information

Karim Benhadji, MD
Taiho Oncology, Inc.
clinicaltrialinfo@taihooncology.com

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