

Population Pharmacokinetic/Pharmacodynamic Modeling of the Effect of Abrocitinib on QT Intervals in Healthy Volunteers

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Abstract

Abrocitinib is a selective Janus kinase 1 inhibitor for the treatment of moderate to severe atopic dermatitis (AD). To assess the relationship between abrocitinib plasma concentrations and heart rate (HR)-corrected QT (QTc) and HR and calculate the effect of abrocitinib on these parameters at suprathreshold concentrations, 36 healthy volunteers received single doses of abrocitinib 600 mg, placebo, and moxifloxacin 400 mg in a 3-period crossover study. The relationship between change from baseline in Fridericia-corrected QTc (Δ QTcF) values and abrocitinib plasma concentrations was modeled using a prespecified linear mixed-effects model. The 90% CIs for time-matched placebo-corrected Δ QTcF (Δ Δ QTcF) were calculated from model parameter estimates and assessed against the regulatory threshold (10 milliseconds) at the predicted suprathreshold concentration in patients with atopic dermatitis (2156 ng/mL). Mean (90%CI) time-matched placebo-corrected change from baseline in HR (Δ Δ HR) was calculated similarly. At the suprathreshold concentration, mean (90%CI) estimates for Δ Δ QTcF and Δ Δ HR were 6.00 (4.52–7.49) milliseconds and 6.51 (5.23–7.80) bpm, respectively. Despite a concentration-dependent effect on Δ QTcF and Δ HR, with statistically significant slopes (90%CI) of 0.0026 (0.0018–0.0035) milliseconds/(ng/mL) and 0.0031 (0.0024–0.0038) bpm/(ng/mL), respectively, abrocitinib does not have a clinically significant effect on QTc interval or HR at suprathreshold exposures.

Keywords

abrocitinib, atopic dermatitis, population exposure-response modeling, QTc interval, suprathreshold exposure

Atopic dermatitis (AD) is a common chronic inflammatory skin disease in which the hallmark symptom is intense pruritus.^{1–5} Moderate to severe AD conveys a significant economic burden, psychosocial comorbidities, and decreased quality of life.⁶ Treatment options for patients with moderate to severe AD unresponsive to topical agents are limited; the introduction of effective systemic therapies for these patients will address an important unmet need.

Abrocitinib is an oral, once-daily Janus kinase 1 selective inhibitor for the treatment of moderate to severe AD in adults and adolescents at 100 and 200-mg once-daily doses. In pivotal phase 3 trials, abrocitinib improved the signs and symptoms of AD, demonstrated rapid improvement in itch, and was well tolerated in patients with moderate to severe AD.^{7–11}

Pharmacokinetic (PK) studies have shown that the abrocitinib plasma maximum serum concentration (C_{max}) and area under the concentration-time curve

increase dose proportionally up to 200 mg.¹² Steady-state plasma concentrations of abrocitinib are achieved

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within 4 days after once-daily administration.¹² Abrocitinib is absorbed with >91% extent of oral absorption and absolute oral bioavailability of $\approx 60\%$.¹³ The peak plasma concentrations of abrocitinib are reached within 1 hour.¹² The metabolism of abrocitinib is mediated by multiple cytochrome P450 (CYP) enzymes, including CYP2C19 ($\approx 53\%$), CYP2C9 ($\approx 30\%$), CYP3A4 ($\approx 11\%$), and CYP2B6 ($\approx 6\%$).¹⁴ In a human radiolabeling study, abrocitinib was the most prevalent circulating species (26%), with 2 active polar monohydroxylated metabolites identified as M1 (3-hydroxypropyl, 11%) and M2 (2-hydroxypropyl, 12%).^{13,15} M1 is less active than abrocitinib, whereas M2 is as active as the parent.¹³ The pharmacologic activity of abrocitinib is attributable to the unbound exposure of the parent molecule ($\approx 60\%$) as well as M1 ($\approx 10\%$) and M2 ($\approx 30\%$) in systemic circulation.^{13,16,17} Abrocitinib is eliminated primarily by metabolic clearance mechanisms. The mean elimination half-lives of abrocitinib and its 2 active metabolites, M1 and M2, range from 3 to 5 hours.^{12,13}

Evaluation of the effect of new non-antiarrhythmic drugs on cardiac repolarization, as detected by heart rate (HR)—corrected time interval from Q wave start to T wave end (QTc) prolongation—is required by regulatory agencies.^{18–20} A thorough QT study was performed with the primary objective to evaluate the relationship between plasma concentrations of abrocitinib in healthy volunteers and 2 electrocardiography-related measures, QTc and HR, and to determine the effect of abrocitinib on QTc and HR at relevant supratherapeutic concentrations in patients with moderate to severe AD.

Methods

Study Design

This study was a phase 1, single-dose, randomized, 3-treatment, 3-period, crossover, placebo-, and positive-controlled trial. The trial protocol, informed consent documentation, and other relevant documents as required were reviewed and approved by the Comité d’Ethique Hospitalo-Facultaire Erasme-ULB, Cliniques Universitaires de Bruxelles (Brussels, Belgium) institutional review board. This study was conducted in the Pfizer Clinical Research Unit (Brussels, Belgium) in accordance with the protocol, legal and regulatory requirements, and general principles per the International Ethical Guidelines for Biomedical Research Involving Human Subjects, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice, and the Declaration of Helsinki. Signed and dated informed consent was required before any study-specific activity was performed.

The sample size for the concentration-QT analysis in healthy volunteers was based on clinical trial simulations using exposure-response characterization from phase 1 data (Pfizer Inc., data on file). The inclusion of 32 subjects would provide $\geq 99\%$ power to detect at least a 5-millisecond difference between moxifloxacin (the positive control) and placebo at the moxifloxacin time to reach the maximum concentration (demonstrating adequate study sensitivity) using clinical trial simulations.

Subjects

Eligible subjects were 18 to 55 years of age at screening; had a body mass index of ≥ 17.5 – ≤ 30.5 kg/m² and a total body weight of >50 kg (110 lb); and had no clinically relevant abnormalities identified by a detailed medical history, full physical examination (including blood pressure and pulse rate measurements), 12-lead electrocardiogram (ECG), and clinical laboratory test results. Subjects who had used prescription/nonprescription drugs and dietary supplements within 7 days or 5 half-lives (whichever was longer) before the first dose of the study drug, herbal supplements/hormone replacement therapy within 7 days before the first dose of the study drug, and/or tobacco or nicotine equivalent to ≥ 5 cigarettes/day were not eligible.

Treatment Received

Crossover treatments consisted of single oral doses of abrocitinib 600 mg, placebo, and moxifloxacin 400 mg. Moxifloxacin served as a positive control to validate the methodology (ie, demonstrate adequate study sensitivity),¹⁸ but moxifloxacin data were not included in the exposure-response analysis. Dosing was separated by a washout period of ≥ 5 days.

Electrocardiography

Triplicate ECG was performed on days 1 and 2 of each treatment period at -1 , -0.5 , and 0 hour before the dose and 0.25, 0.5, 1, 2, 3, 6, 12, and 24 hours after the dose.

Pharmacokinetic Evaluations

Blood samples for PK evaluation were taken at hour 0 and the postdose time points mentioned in the previous section. Abrocitinib concentration values below the level of quantitation (1 ng/mL) have been entered as 0 and included as such in the calculation of means. Plasma samples were stored at -20°C until analysis and assayed at WuXi AppTec (Shanghai, China) using a validated, sensitive, and specific high-performance liquid chromatography–tandem mass spectrometric bioanalytical method.

Abrocitinib and its stable labeled internal standard PF-06651703 were extracted from human plasma

using a liquid-liquid extraction procedure, as described previously.¹³ Following centrifugation, the supernatant was evaporated to dryness, reconstituted, and mixed by vortexing. Separation was achieved after injection onto an Aquasil C18 2.1 × 50 mm, 3 μm column (Thermo Fisher Scientific, Waltham, Massachusetts) using 0.1% formic acid in 1 M ammonium acetate (1/89/10/0.1 v/v/v/v ammonium acetate: water: acetonitrile: formic acid) as mobile phase A; and 0.1% formic acid and 1 M ammonium acetate (1/9/90/0.1 v/v/v/v ammonium acetate: water: acetonitrile: formic acid) as mobile phase B. The samples were analyzed by high-performance liquid chromatography–tandem mass spectrometry using the positive electrospray ionization mode. The mass spectrometer (API 5500; Sciex, Concord, Ontario, Canada) acquisition parameters (precursor ion/product ion) for abrocitinib were 324.4/134.2, and those for internal standard PF-06651703 were 327.2/178.2. The calibration range of the method was 1.00 to 2000 ng/mL, and the quality control concentrations were 3.00 ng/mL (low), 60 ng/mL (medium low), 1000 ng/mL (medium high), 1600 ng/mL (high), and 5000 ng/mL (dilution). The interday assay accuracy ranged from –2.3% to 2.0%, and the between-day precision was ≤7.2%.

Determination of Abrocitinib Supratherapeutic Concentration in Patients With AD

The major route of elimination for abrocitinib is hepatic CYP metabolism, which is predominantly mediated by CYP2C19 and CYP2C9.¹⁴ In a drug-drug interaction (DDI) study with coadministration of fluconazole (a potent CYP2C19 inhibitor and moderate CYP2C9 and CYP3A inhibitor),^{21,22} the adjusted geometric mean of the abrocitinib C_{\max} after coadministration of multiple doses of fluconazole was 1.92-fold higher (90%CI, 1.54–2.39) than the C_{\max} of abrocitinib administered alone.¹⁷ Considering the elimination pathways of abrocitinib, this value (1.92) represents the maximum expected impact on C_{\max} with inhibition of clearance through any intrinsic or extrinsic factors, including renal impairment and organic anion transporter 3 inhibitors, and was therefore used to estimate the supratherapeutic threshold in patients with AD.

The mean therapeutic C_{\max} for patients with AD was predicted using a population PK model.²³ The predicted C_{\max} at steady state after 200-mg once-daily dosing was 1123 ng/mL for adult patients with AD. The predicted C_{\max} value was multiplied by the 1.92-fold increase observed in the fluconazole DDI study¹⁷ to estimate the relevant supratherapeutic C_{\max} —2156 ng/mL—which was used for evaluation of the QTc prolongation potential and effect on HR of abrocitinib in patients with AD.²⁴

Effect of Abrocitinib on ΔHR

All numerical/graphical analysis and mixed-effect modeling were performed in R version 3.4.1. Linear mixed-effect modeling analyses were performed using lme function with the maximum log-likelihood estimation method (method = “ML”) in R. Data manipulation and postprocessing were conducted using R.

A potential effect of abrocitinib on HR was evaluated before correction of the QT interval. The linear relationship between the abrocitinib plasma concentration and HR was evaluated using a prespecified linear mixed-effect model (Equation 1). The intercept and linear slope with drug concentration were estimated as fixed effects. Active treatment was evaluated as a covariate on the intercept to capture any potential drug effect on HR with minimal exposure. The influence of the difference between an individual’s baseline HR and the population mean was also included as a covariate on the intercept to capture the impact. The effect of sampling times was included as a categorical variable to account for diurnal variation:

$$\Delta HR_{ijk} = (\theta_0 + \eta_{0,i}) + (\theta_1 + \eta_{1,i}) C_{ijk} + \theta_2 TRT + \theta_3 \left(HR_{ij0} - \overline{HR_0} \right) + \theta_k + \varepsilon_{ijk} \quad (1)$$

ΔHR_{ijk} is the change from baseline in HR for subject i , in treatment j , at time k ; θ_0 is the population mean intercept in the absence of any covariate effects (thus referring to placebo, at the first postdose sampling time, for a subject with the average baseline HR); θ_1 is the population mean slope of the assumed linear association between concentration and ΔHR ; C_{ijk} is the drug concentration for subject i , in treatment j , at time k (C_{ijk} is 0 for placebo); θ_2 is the covariate effect (treatment-specific intercept) associated with TRT , where TRT is a categorical covariate that takes the value of 0 with placebo and 1 for active treatment; θ_3 is the covariate effect associated with each individual’s baseline HR value (HR_{ij0}) centered on the overall mean of all the baseline HR values ($\overline{HR_0}$); θ_k is the covariate effect associated with each (apart from the first) nominal sampling time k across all treatment phases (ie, for each sampling time, a different covariate effect θ_k is estimated). Random-effect terms referring to interindividual variability were assigned at both the intercept θ_0 and the slope θ_1 terms ($\eta_{0,i}$ and $\eta_{1,i}$, respectively), assuming normal distribution with mean (0,0) and an unstructured variance-covariance matrix Ω ; ε_{ijk} is the random-effect term referring to residual variability in the ΔHR data, assuming normal distribution with mean (0) and variance σ^2 .

In the case of a statistically significant exposure-response relationship between the drug concentration and HR, a study-specific correction factor between the

time interval from peak to peak of 2 neighboring QRS complexes (RR interval) and QT would be estimated using the following linear model:

$$\ln(QT_{ij}) = \ln(\theta_1 + \eta_{1,i}) + (\theta_2 + \eta_{2,i}) \times \ln\left(\frac{RR_{ij}}{1000}\right) + \varepsilon_{ij} \quad (2)$$

Predictions of time-matched placebo-corrected changes from baseline in HR ($\Delta\Delta HR$) with 90%CI at the suprathreshold concentration were derived.

Concentration-QT Analysis

The relationship between the change from baseline in Fridericia-corrected QTc ($\Delta QTcF$) values and abrocitinib plasma concentrations was explored graphically and modeled using the prespecified linear mixed-effect model, similar to abrocitinib plasma concentration and HR in Equation 1.²⁴

$$\Delta QTcF_{ijk} = (\theta_0 + \eta_{0,i}) + (\theta_1 + \eta_{1,i})C_{ijk} + \theta_2 TRT + \theta_3 \left(QTcF_{ij0} - \overline{QTcF_0} \right) + \theta_k + \varepsilon_{ijk} \quad (3)$$

The 2-sided 90%CI for time-matched placebo-corrected $\Delta QTcF$ ($\Delta\Delta QTcF$) was calculated from the model parameter estimates. The upper end of the 90%CI of the mean $\Delta\Delta QTcF$ at the suprathreshold concentration in patients with AD was used to assess whether the QTc prolongation exceeded the regulatory threshold level (10 milliseconds).¹⁹

Results

Thirty-six subjects were randomly assigned to receive treatment in the 3 crossover periods; a total of 864 observations were used in the concentration-QTc analysis. Thirty-one subjects were White, 3 were Black, and 2 were of other ethnicities. Mean age was 33.2 years (range, 19-55 years), mean weight was 80.2 kg (range, 55.8-105.4 kg), and mean body mass index was 24.7 kg/m² (range, 18-30.5 kg/m²). Mean baseline HR ranged from 54.1 to 54.7 bpm, and mean baseline QTcF ranged from 399.2 to 400.7 milliseconds across the treatment groups. Baseline HR and QTcF values across the 3 treatment groups were consistent.

After treatment with moxifloxacin 400 mg, mean changes from time-matched placebo for QTcF ranged from 2.00 to 14.83 milliseconds, with the largest value reported at 2 hours after the dose on day 1. The lower bound of the 2-sided 90%CI for the mean difference between moxifloxacin and placebo for QTcF was >5 milliseconds at 3 hours after a dose of moxifloxacin was given (historic population time to reach the maximum concentration), which deemed the study

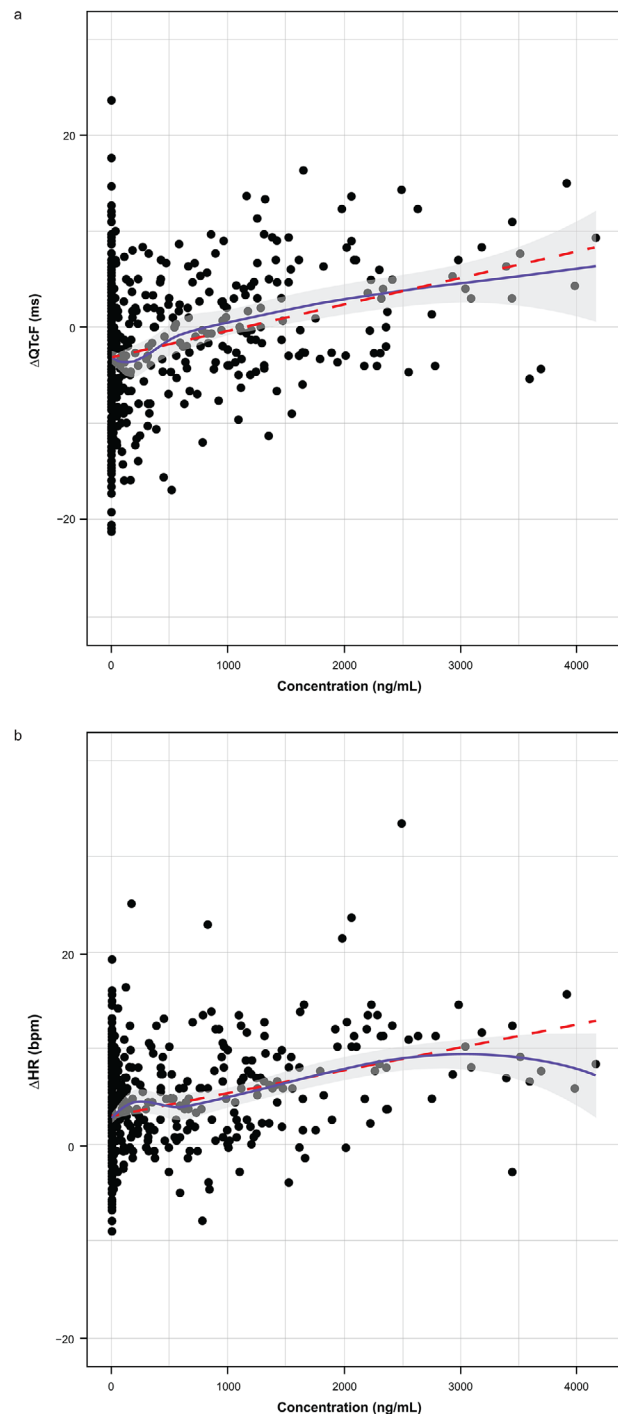


Figure 1. Relationships between abrocitinib plasma concentration and (a) $\Delta QTcF$ and (b) ΔHR . The blue solid lines and the gray areas correspond to the locally estimated scatterplot smoothing and the associated 95%CI, respectively. The red dashed lines denote the linear regression. The black dots correspond to the observed data. $\Delta QTcF$, change from baseline in Fridericia-corrected QT; ΔHR , change from baseline in heart rate.

Table 1. Parameter Estimates for the Concentration- Δ QTcF Modeling

	Estimate	Lower Bound of 90%CI	Upper Bound of 90%CI
θ_0 : intercept (ms)	-0.0062	-1.41	1.398
θ_1 : slope (ms/[ng/mL])	0.0026	0.0018	0.0035
θ_2 : treatment-specific intercept (ms)	0.3141	-0.6115	1.24
θ_3 : baseline effect	-0.0577	-0.1043	-0.0112
θ_4 : time effect (0.5 h) (ms)	-2.678	-4.088	-1.268
θ_5 : time effect (1 h) (ms)	-1.851	-3.281	-0.4212
θ_6 : time effect (2 h) (ms)	-3.152	-4.613	-1.6905
θ_7 : time effect (3 h) (ms)	-2.666	-4.177	-1.155
θ_8 : time effect (6 h) (ms)	-7.052	-8.472	-5.631
θ_9 : time effect (12 h) (ms)	-3.402	-4.796	-2.007
θ_{10} : time effect (24 h) (ms)	-5.103	-6.499	-3.708
η_0 : IIV (intercept)	3.315	2.589	4.245
η_1 : IIV (slope)	0.0014	9×10^{-4}	0.0023
η_0 - η_1 : IIV (intercept-slope correlation)	-0.5294	-0.8032	-0.0707
ε : RV	5.075	4.819	5.345

IIV, interindividual variability; QTcF, Fridericia-corrected time interval from Q wave start to T wave end; RV, residual variability.

Repository artifact ID: RA15490340. Line 1 substituted. Parameter labeling is according to

$$\Delta\text{QTcF}_{ijk} = (\theta_0 + \eta_{0,i}) + (\theta_1 + \eta_{1,i})C_{ijk} + \theta_2\text{TRT} + \theta_3(\text{QTcF}_{ij0} - \text{QTcF}_0) + \theta_k + \varepsilon_{ijk}$$

IIV and RV terms are reported as standard deviations.

methodology adequately sensitive to detect QTc prolongation.

The categorical summaries of ECG data with absolute values and increase from baseline showed that during abrocitinib treatment evaluation, no participant had a maximum QTcF interval >480 millisecond or had an increase from baseline for QTcF values >30 milliseconds.

Model Development and Evaluation

Relationships between the abrocitinib concentrations and Δ QTc and Δ HR are graphically depicted in Figure 1. A linear relationship was seen between the abrocitinib concentration and Δ QTc (Figure 1A); therefore, a linear model was determined to be suitable for analyzing the data. The maximum observed abrocitinib concentration was >4000 ng/mL, which demonstrated that the range of observed concentrations in the study included the predicted supratherapeutic concentration for patients with AD (2156 ng/mL). Model parameter estimates are shown in Table 1. Abrocitinib concentrations had a positive effect on Δ QTcF with a statistically significant slope (ie, the CI does not include 0) of 0.0026 (0.0018-0.0035) millisecond/(ng/mL).

An increasing trend was seen in the Δ HR versus concentration plot (Figure 1B). Model parameter estimates from the linear mixed-effect model are shown in Table 2. Abrocitinib concentrations had a positive effect on Δ HR with a statistically significant slope of 0.0031 (0.0024-0.0038) bpm/(ng/mL).

Graphical evaluation of the Fridericia, Bazett, and estimated study-specific correction factors are shown in Figure 2 using off-treatment data. The Fridericia cor-

rection method ($\beta = 0.333$) was selected for the primary concentration-QTc analysis. The Bazett method ($\beta = 0.5$) overcorrected the trend between the QT and RR intervals. The estimated correction method ($\beta = 0.3375$) using Equation 2 provided a very similar result to the Fridericia correction. The QTc analysis using the estimated correction factor was performed as a confirmatory analysis. Graphical assessments identified no apparent hysteresis or nonlinearity in the relationship between abrocitinib concentrations and the QT or HR effect; the QT effect aligned exactly with the time that the abrocitinib concentration reached its maximum (Figure 3).

Model-Derived Prediction of $\Delta\Delta$ QTcF and $\Delta\Delta$ HR

The model-predicted 90%CI of the mean $\Delta\Delta$ QTcF for the supratherapeutic concentration in patients with AD (2156 ng/mL) was 6.00 (4.52-7.49) milliseconds. The upper bound of the 90%CI was below the regulatory threshold of 10 milliseconds,¹⁹ demonstrating that abrocitinib 200 mg once daily does not have a clinically significant effect on the QTc interval, considering relevant “worst-case” supratherapeutic exposures for patients with AD that account for reduced clearance due to DDI.

The model-predicted mean $\Delta\Delta$ QTcF and $\Delta\Delta$ HR, along with the associated 90%CIs at supratherapeutic exposures, are summarized in Table 3. The mean model-predicted $\Delta\Delta$ QTcF (90%CI) across the studied concentration range is shown in Figure 4. The mean model-predicted $\Delta\Delta$ HR across the studied concentration range is shown in Figure 5. The mean $\Delta\Delta$ HR (90%CI) at the supratherapeutic concentration in

Table 2. Parameter Estimates for the Concentration- Δ HR Modeling

	Estimate	Lower Bound of 90%CI	Upper Bound of 90%CI
θ_0 : intercept (bpm)	-0.669	-1.485	0.1466
θ_1 : slope (bpm/[ng/mL])	0.0031	0.0024	0.0038
θ_2 : treatment-specific intercept (bpm)	-0.1979	-0.7999	0.4041
θ_3 : baseline effect	-0.1544	-0.2126	-0.0963
θ_4 : time effect (0.5 h) (bpm)	0.0797	-0.8296	0.9891
θ_5 : time effect (1 h) (bpm)	-0.299	-1.222	0.6243
θ_6 : time effect (2 h) (bpm)	-0.7794	-1.724	0.1652
θ_7 : time effect (3 h) (bpm)	-0.5218	-1.500	0.4569
θ_8 : time effect (6 h) (bpm)	5.689	4.774	6.605
θ_9 : time effect (12 h) (bpm)	4.274	3.377	5.172
θ_{10} : time effect (24 h) (bpm)	3.111	2.213	4.009
η_0 : IIV (intercept)	1.594	1.193	2.13
η_1 : IIV (slope)	0.0016	0.0011	0.0023
η_0 - η_1 : IIV (intercept-slope correlation)	-0.4389	-0.7039	-0.0668
ε : RV	3.264	3.096	3.441

HR, heart rate; IIV, interindividual variability; RV, residual variability.

Repository artifact ID: RA15490341. Line 1 substituted. IIV and RV terms are reported as standard deviations. Parameter labeling is according to $\Delta HR_{ijk} = (\theta_0 + \eta_{0,i}) + (\theta_1 + \eta_{1,i})C_{ijk} + \theta_2 TRT + \theta_3(HR_{ij0} - \bar{HR}_0) + \theta_k + \varepsilon_{ijk}$

Table 3. Model-Predicted Mean $\Delta\Delta$ QTcF and $\Delta\Delta$ HR Along With the Associated 90%CIs at Supratherapeutic Exposures

Population	Concentration (ng/mL)	Mean $\Delta\Delta$ QTcF (90%CI) (ms)	Mean $\Delta\Delta$ HR (90%CI) (bpm)
Healthy volunteers	1701	4.8 (3.63–5.98)	5.1 (4.09–6.11)
Patients with AD	2156	6.0 (4.52–7.49)	6.5 (5.23–7.80)

AD, atopic dermatitis; $\Delta\Delta$ HR, time-matched placebo-corrected change from baseline in heart rate; $\Delta\Delta$ QTcF, time-matched placebo-corrected change from baseline in Fridericia-corrected QT.

patients with AD was 6.51 (5.23-7.80) bpm, which is <10 bpm; therefore, the Fridericia correction is considered appropriate.²⁴

Discussion

This PK/pharmacodynamics analysis demonstrates that abrocitinib does not have a clinically significant effect on QTc interval or HR, even when considering worst-case supratherapeutic exposures at the 200 mg once-daily dose in patients with moderate to severe AD after accounting for the maximum expected impact on C_{max} with inhibition of clearance through any intrinsic or extrinsic factors. In this concentration-QTc analysis after a single abrocitinib dose of 600 mg, the upper bound of the 90%CI for the $\Delta\Delta$ QTc interval was below the relevant regulatory threshold of 10 milliseconds.¹⁹ The results of the current study support the safety profile of abrocitinib 200 mg once daily. In addition, ECG monitoring in pivotal phase 3 clinical trials of abrocitinib in patients with moderate to severe AD showed no clinically meaningful cardiac changes.^{7,11}

Delayed cardiac repolarization is a major reason for delayed or rejected regulatory approval or removal of

drugs from the market.¹⁸ Thorough QT/QTc (TQT) studies are conducted in healthy volunteers to ensure the cardiac safety of drugs in development. Because the AD population does not have any known cardiac differences compared with healthy volunteers, assessment of the QT interval in healthy volunteers is expected to be applicable to the AD population. Abrocitinib has a relatively short half-life; therefore, a single dose for this analysis was appropriate.¹²

The cardiovascular effects of abrocitinib and its active metabolites, M1 and M2, have been assessed using human ether à-go-go-related gene (hERG) and Nav1.5 channels in vitro. For abrocitinib and its metabolites, M1 and M2, the exposure margins for (hERG) channel inhibition ranged between 76 to 968 \times and 27 to 610 \times relative to steady-state human unbound and total C_{max} , respectively, at the 200-mg once-daily clinical dose; the corresponding exposure margins for the Nav1.5 channel assay ranged between 240 and 323 \times and 86 to 203 \times , respectively (data on file). Based on the high exposure margins, the potential for both abrocitinib and metabolites to have a QTc prolongation effect in vivo is very low, and they are very unlikely to have bona fide proarrhythmic effects in humans. In addition, the metabolism

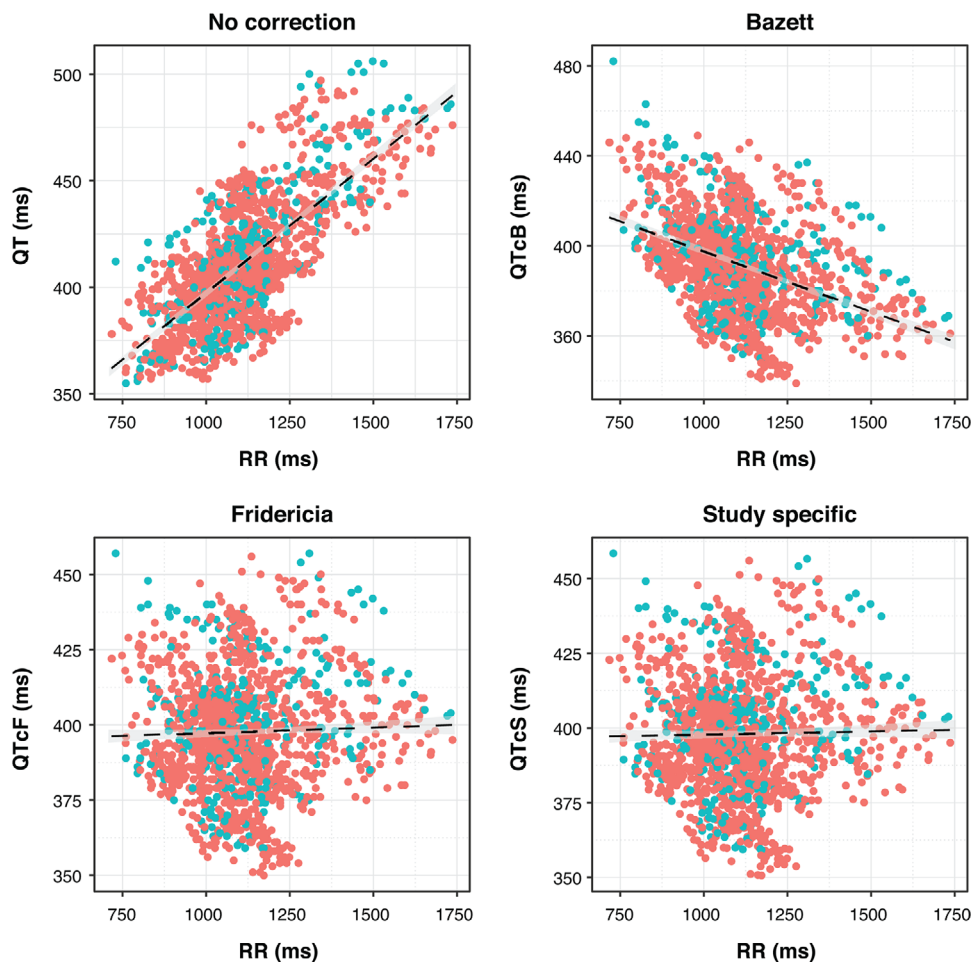


Figure 2. Plot of individual QT, QTcB, QTcF, and QTcS versus R-R interval for off-treatment data. Cyan dots correspond to data from baseline of the abrocitinib period; coral dots correspond to placebo data. Black dashed lines and the gray area around them refer to the linear regression across all data and the associated 95%CI, respectively. QT, time interval from Q wave start to T wave end; QTcB, Bazett-corrected QT; QTcF, Fridericia-corrected QT; QTcS, study-specific corrected QT; RR, time interval between peaks of 2 neighboring QRS complexes.

of M1 and M2 are formation rate limited.¹³ Inclusion of metabolites in the QTc modeling analysis would not provide any further information to evaluate the effect on the QTc interval. The exploratory plots evaluating the delay between drug concentration and the effect on QTc (Figure 3) also showed no apparent hysteresis. With these considerations, the active metabolites of abrocitinib, M1 and M2, were not analyzed or modeled in this study. A linear mixed-effect model was used in this concentration-QTc analysis, assuming that there is a direct response relationship between the systemic exposure of abrocitinib and the effect on cardiac repolarization, which is supported by the graphical assessments for hysteresis or nonlinearity (Figures 1 and 2). The linear mixed-effect model was also pre-specified in accordance with the regulatory guidelines and white paper recommendations.^{19,24} There is high confidence for the derivation of the estimated effect of

abrocitinib on the QTc interval because the assessment was conducted at the supratherapeutic concentration representing a worst-case condition: maximum inhibition of the clearance pathway of abrocitinib.

Data from the healthy volunteers in this study were applied to the AD population by use of a scaling factor. This extrapolation relied on a well-conducted PK analysis using data from 11 clinical trials (Pfizer Inc., data on file). These findings represent an effective use of a population PK model developed to describe parameters in the AD population. Based on the population PK model, the C_{max} increases were less than proportional with doses >400 mg. Therefore, the abrocitinib 600-mg dose used in this QT study did not provide 3-fold exposure as expected, compared with the highest therapeutic dose of abrocitinib (200 mg). Nevertheless, adequate exposure representative of relevant supratherapeutic peak concentrations, expected as a result of

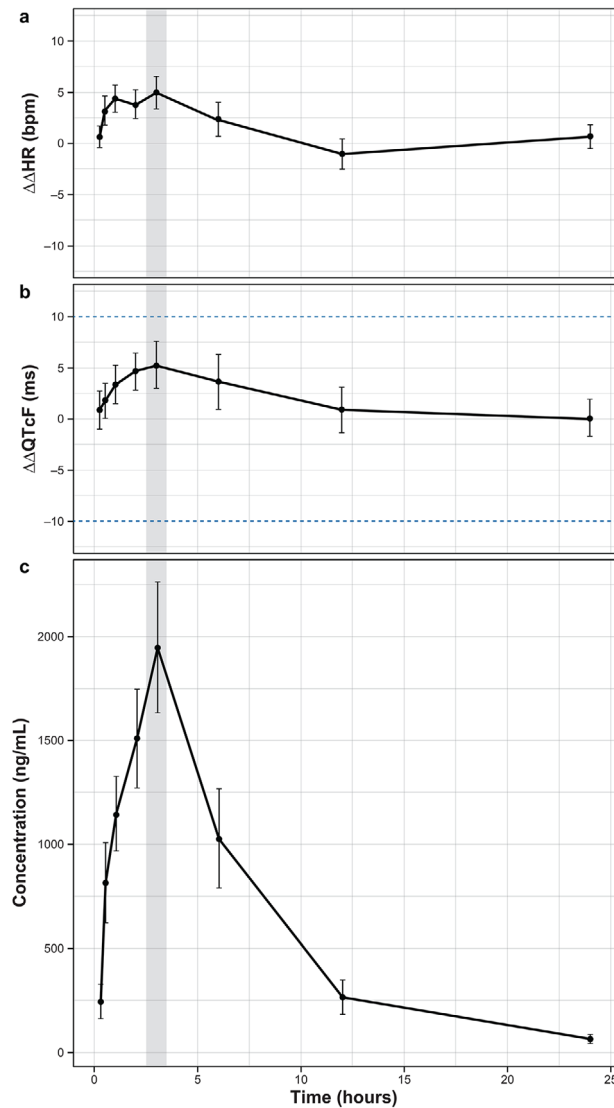


Figure 3. No time delay between abrocitinib concentrations and QT effects. (a) $\Delta\Delta$ HR-time profile. (b) $\Delta\Delta$ QTcF-time profile. (c) Mean concentration-time profile. Error bars correspond to 90% CIs around the mean. Horizontal dashed blue lines highlight a change of 10 milliseconds, a magnitude that can be considered clinically significant. $\Delta\Delta$ QTcF, time-matched placebo-corrected change from baseline in Fridericia-corrected QT.

the 1.92-fold increase due to metabolic interaction with fluconazole at the 200-mg once-daily dose in patients with AD,¹⁷ was obtained in this QT study to complete evaluations.

In conclusion, oral administration of abrocitinib 100 or 200 mg once daily in patients with moderate to severe AD does not have a clinically significant effect on the QTc interval or on HR, even considering relevant worst-case suprathreshold exposures accounting for the maximum expected impact on C_{max} with inhibition of hepatic clearance through any intrinsic or extrinsic

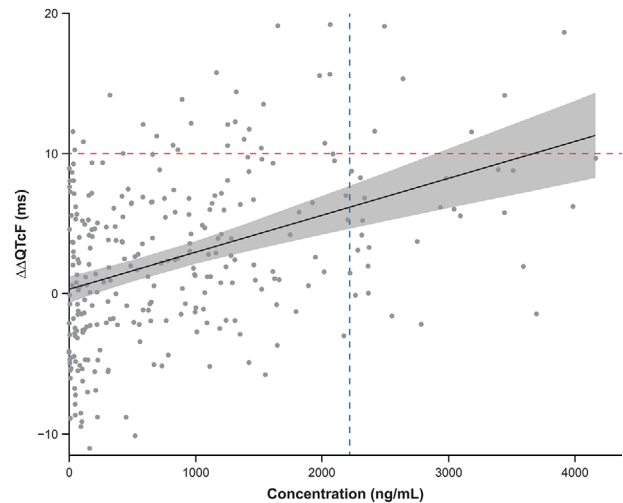


Figure 4. Mean model-predicted $\Delta\Delta$ QTcF (90%CI) across the studied concentration range. The R-squared value of the linear mixed-effects model is 0.44. The black solid line corresponds to the predicted mean $\Delta\Delta$ QTcF across the studied concentration range, and the gray area corresponds to the associated 90% CIs. Black dots represent individual observations (corrected by population prediction of placebo effect). The horizontal dashed red line highlights a change of 10 milliseconds, a magnitude that can be considered clinically significant. The vertical dashed blue line represents the suprathreshold concentration in patients with AD (2156 ng/mL). AD, atopic dermatitis; $\Delta\Delta$ QTcF, time-matched placebo-corrected change from baseline in Fridericia-corrected QT.

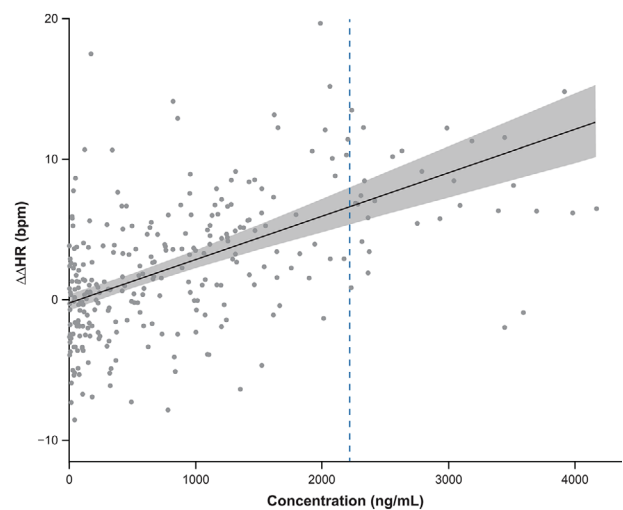


Figure 5. Mean model-predicted $\Delta\Delta$ HR across the studied concentration range. The R-squared value of the linear mixed-effect model is 0.56. The black solid line corresponds to the predicted mean $\Delta\Delta$ HR across the studied concentration range, and the gray area corresponds to the associated 90% CIs. Black dots represent individual observations (corrected by population prediction of placebo effect). The vertical dashed blue line represents the suprathreshold concentration in patients with AD (2156 ng/mL). AD, atopic dermatitis; $\Delta\Delta$ HR, time-matched placebo-corrected change from baseline in heart rate.

factors. Based on the conclusions of this study, clinically relevant doses of abrocitinib are not likely to be associated with a risk for severe cardiac adverse events related to QTc prolongation in patients with moderate to severe AD, including those who may take strong CYP2C19 inhibitors concomitantly and may represent worst-case suprathreshold concentrations of abrocitinib.

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Conflicts of Interest

All authors are employees and shareholders of Pfizer, Inc.

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Author Contributions

X.W. contributed to performing the analysis and interpretation of data and drafted the report. P.G., S.A.F., and V.H.L. contributed to study design and interpretation of data and reviewed the report. B.K.M., J.W., A.M., and T.N. contributed to interpretation of data and reviewed the report.

Data Sharing

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual deidentified participant data. See <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information.

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