Lack of Electrocardiographic Effects of Deucravacitinib in Healthy Subjects

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Abstract

Deucravacitinib is a novel, oral, selective inhibitor of the intracellular signaling kinase tyrosine kinase 2. This phase 1, randomized, partially double-blind, 4-period crossover study in healthy adults was conducted to determine whether deucravacitinib 12 mg (therapeutic dose) or 36 mg (supratherapeutic dose) had a clinically relevant effect on the corrected QT interval and other electrocardiographic (ECG) parameters. Subjects received 1 of 4 sequences of placebo, deucravacitinib 12 mg, deucravacitinib 36 mg, and moxifloxacin 400 mg (positive control) in a randomized crossover fashion. The placebo-corrected change from baseline for the QT interval corrected for heart rate using the Fridericia method (QTcF), ECG parameters, and safety measures were evaluated. A clinically meaningful QTcF prolongation of >10 milliseconds was not found for deucravacitinib at tested doses. Assay sensitivity was demonstrated by the observation of known QT effects of moxifloxacin in the study. Deucravacitinib had no clinically relevant effect on other parameters and was generally well tolerated. The majority of adverse events (AEs) were mild, and all AEs resolved by study's end. Three treatment-related serious AEs of pharyngitis, cellulitis, and lymphadenopathy occurred in 1 subject following administration of deucravacitinib 12 mg, but resolved by end of study. This study demonstrated that a single oral dose of deucravacitinib 12 or 36 mg did not produce a clinically relevant effect on the corrected QT interval or other measured ECG parameters in healthy adults.

Keywords

cardiovascular, clinical pharmacology, dermatology, drug metabolism, electrocardiography, pharmacokinetics

Deucravacitinib is a novel, oral, selective tyrosine kinase 2 inhibitor that is involved in the signaling of proinflammatory cytokines such as interleukin-23 and type I interferons.[1] Binding of deucravacitinib to the pseudokinase domain of tyrosine kinase 2 confers greater functional selectivity than that of inhibitors of other closely related kinases that bind to the more highly conserved active adenosine triphosphate–binding site of the enzyme.[1,2] The structure of deucravacitinib has been reported previously (Figure 1).[3]

In human pharmacokinetic (PK) studies, deucravacitinib absorption was rapid (time of maximum observed plasma concentration [t_{max}], 1 hour), near complete (99%), and consistent (mean terminal-phase half-life [$t_{1/2}$] range, 7-15 hours).[4–6] Following oral administration of deucravacitinib tablets, exposure increased in a dose-proportional manner,[6] and elimination was through multiple clearance pathways, including renal, fecal, and metabolic elimination (via cytochrome P450 1A2, carboxylesterase 2, and uridine glucuronyl transferase, among others).[4–6] Minimal decreases in the geometric maximum observed plasma concentration (C_{max}) or area under the plasma concentration–time curve (AUC) of deucravacitinib occurred after pretreatment with an H_2-receptor antagonist or a proton pump inhibitor and after coadministration with medications that affect various drug-metabolizing enzymes and transporters (eg, cyclosporine, fluvoxamine, ritonavir, pyrimethamine, or diflunisal).[6,7] Following coadministration of deucravacitinib with commonly used

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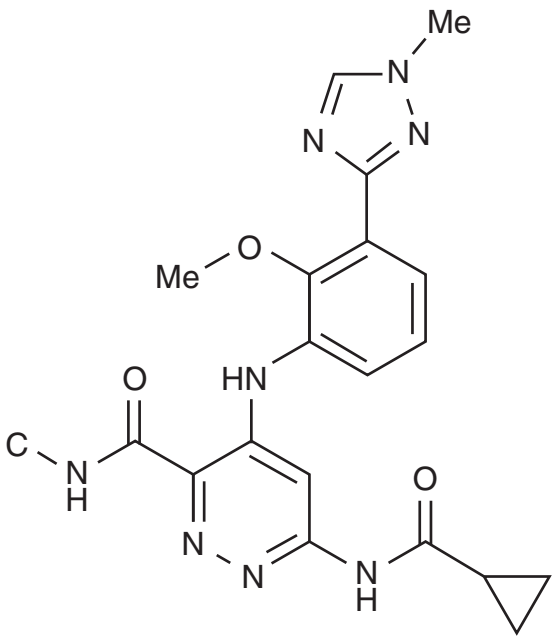

Figure 1. Structure of deucravacitinib. Reprinted with permission from Wrobleski ST, Moslin R, Lin S, et al. Highly selective inhibition of tyrosine kinase 2 (TYK2) for the treatment of autoimmune diseases: discovery of the allosteric inhibitor BMS-986165. *J Med Chem*. 2019;62:8973-8995.[3] Copyright 2021 American Chemical Society.

concomitant medications (eg, rosuvastatin, norethindrone, ethinyl estradiol, methotrexate, and mycophenolate mofetil), deucravacitinib did not have a meaningful impact on the exposures of these medications.[3,4,6,8]

Deucravacitinib was shown to be efficacious and generally well tolerated in a phase 2 trial in moderate to severe plaque psoriasis at doses of ≥3 mg once daily.[9] In a phase 2 study of patients with active psoriatic arthritis, deucravacitinib was efficacious and had a safety and laboratory parameter profile that was consistent with that seen in the phase 2 psoriasis trial.[9,10] In vitro data did not indicate any meaningful inhibition of cardiac electrophysiologic ion channels by deucravacitinib at clinically relevant doses and exposures. This thorough QT/QTc (TQT) study investigated whether deucravacitinib at a therapeutic dose of 12 mg or at the 3-fold higher supratherapeutic dose of 36 mg had a clinically relevant effect on cardiac repolarization as measured by the QT interval corrected for heart rate (HR).

Methods

This was a randomized, phase 1, partially double-blind (blinded for active treatments and placebo control, unblinded for positive control [moxifloxacin]), 4-period crossover, multidose study in healthy subjects. This single-center study at PRA Health Sciences, (Lenexa, Kansas) was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The protocol and informed consent forms were approved by an institutional review board (Advarra, Columbia, Maryland) before study initiation. Subjects provided written informed consent.

Subjects

Subjects were assessed for eligibility ≤28 days before admission to the study center (day −1). Subjects were eligible if they were 18 to 50 years of age, had a body mass index of 18 to 32 kg/m^2, and body weight ≥50 kg at screening. Eligible subjects had to have no clinically significant deviations from normal electrocardiographic (ECG) findings, and no clinically significant medical histories or clinical laboratory determinations. The following 12-lead ECG findings were required for eligibility: QTcF <450 milliseconds, QRS interval <120 milliseconds, QT interval <500 milliseconds, PR interval <210 milliseconds, and HR ≥45 beats per minute (bpm).

Subjects were excluded for any of the following: history of clinically relevant cardiac disease; arrhythmias, presyncope, or syncopal episodes; heart failure or other risk factors for torsades de pointes; history of hypokalemia; history (personal or family) of prolonged QT interval; family history of sudden cardiac death at a young age; or second- or third-degree heart block at screening or baseline (day −1). The use of concomitant medications that prolong the QT/QTc interval within 4 weeks or 5 half-lives of deucravacitinib (3 days) before study treatment administration was also exclusionary, as was the presence of an autoimmune disorder, immunodeficiency, or conditions associated with immunocompromise.

Study Design

Eligible subjects were randomly assigned to 1 of the following treatment sequences on day 1:

- Placebo, deucravacitinib 12 mg, deucravacitinib 36 mg, moxifloxacin
- Moxifloxacin, deucravacitinib 36 mg, deucravacitinib 12 mg, placebo
- Deucravacitinib 12 mg, moxifloxacin, placebo, deucravacitinib 36 mg
- Deucravacitinib 36 mg, placebo, moxifloxacin, deucravacitinib 12 mg

During the study, concomitant medications were not allowed unless they were prescribed to treat specific clinical events. The study design is shown in Figure 2. Study treatments were administered orally after a 10-hour fast and were followed by a 4-hour fast. The treatments were administered orally at the beginning of each period (dosing on days 1, 6, 11, and 16), after

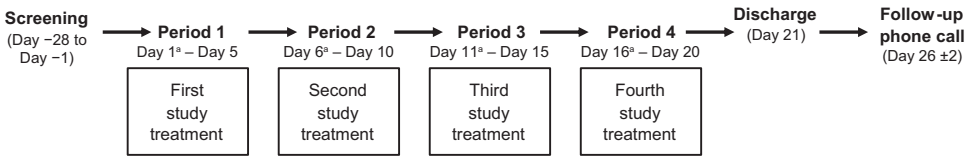

Figure 2. Study design. [a]ECG measurements and PK sampling were performed on days 1, 6, 11, and 16. ECG, electrocardiographic; PK, pharmacokinetics.

a 5-day washout (equivalent to an excess of 7 half-lives or 3.8 days). Following discharge on day 21, subjects were contacted by phone for follow-up 5 days later.

Study Drugs

Deucravacitinib and placebo tablets were indistinguishable from each other, allowing for double blinding for those treatments. The treatments were administered as 3 placebo tablets (placebo), 1 deucravacitinib 12-mg tablet and 2 placebo tablets (therapeutic), or 3 deucravacitinib 12-mg tablets (supratherapeutic), all of which were identical in appearance. Double blinding was not possible for moxifloxacin 400 mg (positive control) because it had a different appearance than the deucravacitinib and placebo tablets. To maintain blinding of study staff, and because moxifloxacin could not be adequately blinded, all study treatments were administered by study staff not involved in the collection of study assessments.

Cardiodynamic ECG Assessments

Continuous Holter monitor recordings were performed after subjects rested in a supine or semirecumbent position for 10 minutes. Up to 10 replicate, 14-second digital 12-lead ECG tracings were extracted from continuous Holter recordings using the TQT Plus method (iCardiac Technologies, Philadelphia, Pennsylvania). HR stability is a known determinant of QT variability.[11] TQT Plus selects ECG recordings with minimal HR variability and noise through algorithms that integrate analysis and statistical quality control.[11,12] A stable HR range, as defined in the TQT Plus method, has <10% variation in beat-to-beat RR interval.[11] The ECG recordings that meet this criterion within the protocol-specified extraction time window are then selected and classified into high or low confidence rank, based on quality metrics including beat stability, HR changes, noise, and other parameters.[11,12] The TQT plus method is used in high-precision ECG measurement, which produces substantially less variability in QT measurements compared with semiautomated methods of measuring ECG intervals.[11] The protocol-specified time points were −1.0, −0.75, −0.5, and 0 hours before dosing and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 10, 12, and 24 hours after dosing on days 1, 6, 11, and 16. ECGs were assessed by an independent ECG core laboratory (eResearch Technology, Philadelphia, Pennsylvania) blinded to time and treatments.

Pharmacokinetic Assessments

Blood samples (<500 mL total per subject during the study) for PK assessment were collected on days 1, 6, 11, and 16, at 0 hours before dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 10, 12, 24, 36, 48, 72, and 96 hours after dosing. Plasma was analyzed by an independent bioanalytic laboratory (Q^2 Solutions, Ithaca, New York) using a validated liquid chromatography system with tandem mass spectrometry.

The following PK parameters were measured or calculated for deucravacitinib: C_{max}, t_{max}, AUC from time 0 to last quantifiable concentration, AUC from time 0 extrapolated to infinite time, and $t_{1/2}$. Values of PK parameters for each subject were obtained by noncompartmental methods using a validated PK analysis program (Phoenix WinNonlin version 8.1; Certara, Princeton, New Jersey).

Liquid Chromatography

The plasma was separated from blood using dipotassium ethylenediaminetetraacetic acid as an anticoagulant. The internal standards for deucravacitinib and moxifloxacin were BMT-143848-03 (stable isotope–labeled deucravacitinib) and moxifloxacin-d_4. Deucravacitinib was extracted from the plasma using a liquid-liquid extraction technique, and moxifloxacin was extracted from plasma using protein precipitation. Deucravacitinib was eluted on an Acquity UPLC HSS T3 column (2.1 × 50 mm, 1.8 μm) (Waters Corporation, Milford, Massachusetts) for chromatographic separation at a flow rate of 600 μL/min at 60°C in 50-μL aliquots. Chromatographic separation of moxifloxacin was performed using the Thermo Hypersil Gold C_{18} column (2.1 × 50 mm, 5 μm; Thermo Fisher Scientific, Waltham, Massachusetts) at a flow rate of 600 μL/min at room temperature.

Mass Spectrometry

The liquid chromatography with tandem mass spectrometry system for deucravacitinib and moxifloxacin consisted of an API 4000 with the TurboIonSpray (AB Sciex LLC; Framingham, Massachusetts) interface operated in the positive ion mode. Quantitation was

performed by selected reaction monitoring (m/z 426.2 → m/z 358.2 for deucravacitinib; m/z 431.2 → m/z 359.2 for BMT-143848-03; m/z 402.2 → m/z 358.3 for moxifloxacin; m/z 406.2 → m/z 362.2 for moxifloxacin-d_4).

Linear regression analysis was conducted using a weighting of $1/x^2$. The calibration ranges were 0.5 ng/mL (lower limit of quantitation) to 500 ng/mL (upper limit of quantitation) for deucravacitinib and 25.0 ng/mL (lower limit of quantitation) to 5000 ng/mL (upper limit of quantitation) for moxifloxacin.

Assessment of assay performance for deucravacitinib indicated between-run precision of ≤0.6% coefficient of variation, within-run precision of ≤2.6% coefficient of variation, and accuracy of ±4.8% mean percent deviation from nominal concentration. The assay performance was also assessed for moxifloxacin (≤1.8%, ≤2.2%, and ±4.0%, respectively).

Safety

Adverse events (AEs), clinical laboratory tests (clinical chemistry, hematology, and urinalysis), safety 12-lead electrocardiogram (HR, PR interval, QRS duration, QT interval, and QTcF), vital signs (blood pressure, HR, temperature, and respiratory rate), and physical examination findings were recorded at selected times throughout the study.

Statistical Analyses

The analysis was based on exposure-response modeling of the relationship between deucravacitinib and its metabolites and placebo-corrected change from baseline QTcF (ΔΔQTcF) with the intent to exclude an effect of >10 milliseconds at clinically relevant plasma drug concentrations. The analysis was performed using the PK/QTc analysis set. This was defined as all subjects in both the PK and QT/QTc analysis sets with at least 1 pair of postdose PK and QTcF data from the same time point for that study treatment (deucravacitinib or moxifloxacin). Baseline QTcF was the mean of 4 predose values (collected at −1.0, −0.75, −0.5, and 0.0 hours before dosing) at the start of each treatment period, that is, days 1, 6, 11, and 16. Change from baseline QTcF is denoted as ΔQTcF, and for placebo correction, the individual ΔQTcF for placebo calculated at a specific time point was subtracted from ΔQTcF for the same subject taking deucravacitinib at the same time point to generate ΔΔQTcF.

Modeling began with a single full model including ΔΔQTcF as the dependent variable, time-matched plasma concentrations of each analyte (deucravacitinib and its metabolites, BMT-153261 and BMT-158170) as the covariates, centered baseline QTcF as an additional covariate, and subject as a random effect for both intercept and slopes, when applicable. The following linear mixed effects model was considered:

$$\Delta\Delta QTcFik = \mu 0 + \mu i + \theta 0 \times BQTc,I + (\eta 01 + \eta i1)\, Cik1 + (\eta 02 + \eta i2)\, Cik2 + (\eta 03 + \eta i3)\, Cik3 + \varepsilon ik$$

where i is the ith subject; k is the kth time point; $BQTc,i$ is the centered baseline QTcF for the ith subject; $Cik1$, $Cik2$, and $Cik3$ are the concentrations of deucravacitinib, BMT-153261, and BMT-158170 at the kth time point for subject I; $\mu 0$ and $\eta 01$, $\eta 02$, and $\eta 03$ are the fixed intercept and slopes, respectively; and μi and $\eta i1$, $\eta i2$, and $\eta i3$ are the subject-specific random effects for the intercept and slopes, respectively, having mean [0,0,0,0] and unstructured covariance matrix. The error term εik is assumed to be independent and identically distributed (iid) normal $N(0, \sigma 2)$. The model selection procedure among the full model and reduced models from possible first-order combinations (without quadratic and interaction terms) among the 3 analytes (including models with only 1 analyte and with any 2 analytes) was conducted by using Akaike information criterion and the t value for the intercept estimator.[13] After the model selection procedure, the final model included the parent analyte (deucravacitinib) only. To assess the appropriateness of a linear model, normal quantile-quantile (Q-Q) plots for the standardized residuals and random effects, along with other residual plots, were used.

Assay sensitivity was demonstrated using an exposure-response analysis of the effect of moxifloxacin on ΔΔQTcF using a model similar to the one used for deucravacitinib. Assay sensitivity was demonstrated if the slope of the exposure-response relationship was statistically significant at 10% level of significance in a 2-sided test, and the predicted QT effect (ie, the lower bound of the 2-sided 90%CI) was >5 milliseconds at the observed geometric mean C_{max} of 400 mg moxifloxacin.

Analyses of the effect of 12 and 36 mg deucravacitinib on ΔΔQTcF, ΔΔHR, ΔΔPR, and ΔΔQRS were evaluated at each postdose time point. The QT/QTc analyses set, defined as all subjects in the safety analysis set with measurements at baseline and at least 1 postdose time point with a valid ΔQTcF measurement, was used for the analyses of assay sensitivity and the effect of moxifloxacin on ΔΔQTcF and for the categoric analysis of ECG parameters, QTcF, HR, PR, and QRS. Frequency of abnormalities in T-wave morphology and U-wave presence were analyzed versus baseline.

Safety was analyzed descriptively using the safety set, which was defined as all randomized subjects who took at least 1 dose of deucravacitinib, placebo, or moxifloxacin. Descriptive statistics were also used to

Table 1. Baseline ECG Values[a]

	Placebo (n = 39)	Deucravacitinib 12 mg (n = 39)	Deucravacitinib 36 mg (n = 39)	Moxifloxacin (n = 40)
QTcF, ms				
Mean (SD)	400.1 (12.90)	400.2 (13.02)	399.3 (14.69)	400.4 (13.70)
90%CI	396.61-403.57	396.66-403.69	395.31-403.25	396.76-404.06
Median	402.3	402.7	400.9	402.0
Min, max	372, 431	370, 429	371, 437	371, 433
HR, bpm				
Mean (SD)	62.3 (7.75)	62.5 (7.65)	61.7 (7.13)	63.5 (7.40)
90%CI	60.21-64.39	60.40-64.53	59.82-63.67	61.49-65.43
Median	61.0	61.6	61.1	64.4
Min, max	51, 81	48, 82	51, 80	48, 84
PR interval, ms				
Mean (SD)	149.6 (16.99)	149.2 (17.61)	147.5 (17.65)	148.6 (16.73)
90%CI	144.98-154.15	144.49-153.99	142.76-152.29	144.12-153.03
Median	150.3	148.5	145.8	147.3
Min, max	113, 186	116, 183	110, 188	112, 189
QRS interval, ms				
Mean (SD)	104.2 (4.13)	104.1 (4.11)	104.0 (3.76)	104.6 (4.36)
90%CI	103.06-105.29	103.02-105.24	102.97-105.00	103.44-105.76
Median	103.9	104.0	104.3	104.0
Min, max	98, 113	97, 113	96, 113	96, 112

bpm, beats per minute; ECG, electrocardiogram; HR, heart rate; QTcF, QT interval corrected for heart rate using the Fridericia method.
[a] Baseline values were calculated from the predose values of the 4 treatments (placebo, deucravacitinib [12 and 36 mg], and moxifloxacin) recorded on days 1, 6, 11, and 16 in each corresponding treatment period.

summarize plasma concentrations. The PK analysis set consisted of all randomized subjects who received at least 1 dose of deucravacitinib or moxifloxacin and had at least 1 evaluable PK concentration. PK parameters were calculated for deucravacitinib only. When summarizing plasma concentrations, values below the limit of quantitation were set to 0.

Sample Size Calculations

The target sample size of 40 (10 per treatment sequence) was selected to ensure that there would be 32 evaluable subjects from all treatment periods. Assuming QTc effects of 3 milliseconds for deucravacitinib and 0 milliseconds for placebo, a standard deviation of ΔQTcF of 8 milliseconds for each treatment, and a conclusion of "no effect" if the 90%CI of placebo-corrected ΔQTc is <10 milliseconds, a sample size of 32 subjects would provide >95% power (1-sided alpha = 5%) in a paired *t* test for equivalence. With a sample size of 32 subjects, an effect size of 0.59, which translates to ΔQTcF having a variability of standard deviation <7.5 milliseconds, would guarantee at least 95% power in a 1-sided *t* test when demonstrating assay sensitivity.

Results

Subjects

A total of 40 subjects were randomized and received study treatment, and 38 subjects completed the study. The majority of subjects (mean age, 33 years) were men (70%) and Black/African American (68%). Baseline ECG values were within expectations for a healthy population (Table 1). Two subjects discontinued from the study; 1 subject discontinued due to an AE (elevated blood creatine phosphokinase [CPK]), considered unrelated to the study drug after receiving moxifloxacin and deucravacitinib 36 mg as treatments. In this subject, elevated CPK was noted predose in period 2 (day 6). After the subject received the planned period 2 study treatment, CPK levels remained >10 times the upper limit of the reference range through day 11 and decreased to 503 U/L by early termination on day 16. The subject therefore did not receive the period 3 and 4 treatments. The other subject discontinued at the investigator's discretion due to the subject's disorderly conduct; the subject had received all treatments except deucravacitinib 36 mg before discontinuation.

Concentration-QTc Modeling

The primary model following model selection and evaluation included only 1 analyte, deucravacitinib (parent) because it has the smallest Akaike information criterion value (5496.9) relative to models with other analytes. The predicted ΔΔQTcF values of the proposed model of concentration-QTc for deucravacitinib were close to observed values (Figure 3). Additionally, model evaluation plots like the normal Q-Q plots of the standardized residuals and Q-Q plots of the random effects (data not shown) do not show any

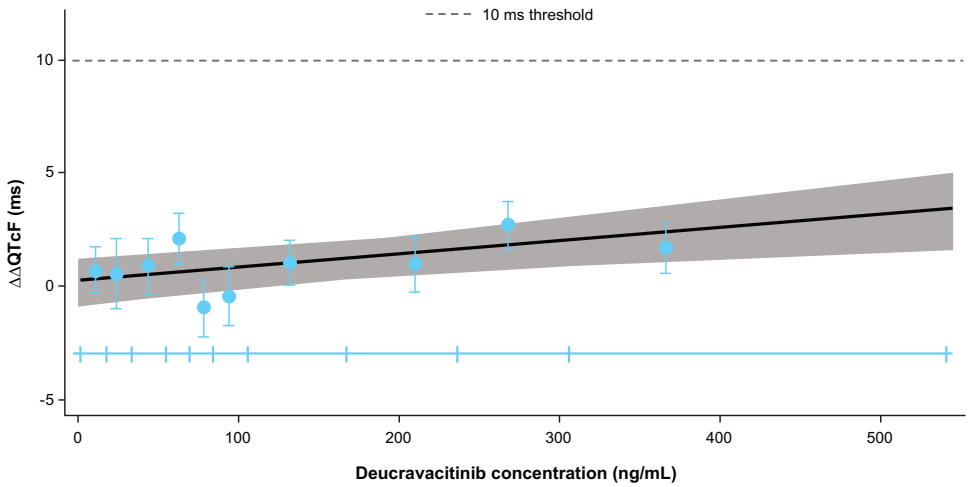

Figure 3. Model-predicted ΔΔQTcF[a] and observed ΔΔQTcF[b] across plasma concentrations for deucravacitinib. [a]Prediction was based on the model ΔΔQTcF = 0.19 + [deucravacitinib concentration • 0.0059]. [b]Observed mean ΔΔQTcF with 90%CI are displayed at the median plasma concentration within each decile for deucravacitinib. The solid line with shaded area denotes the model-predicted mean ΔΔQTcF with 90%CI. The horizontal line with notches shows the range of concentrations divided into deciles for deucravacitinib. The distance between each decile represents the point at which 10% of the data are present (eg, the first notch to second notch denotes the first 10% of the data). QTcF, QT interval corrected for heart rate using the Fridericia method; ΔΔQTcF, placebo-corrected change from baseline QTcF.

significant violations of the normality assumption for the within-subject errors and the random effects, respectively. Therefore, the model was considered a reasonable representation of the relationship between ΔΔQTcF and concentration for deucravacitinib. The estimated population slope of the model was 0.0059 milliseconds per ng/mL (90%CI, 0.0021-0.0098; P = .014) with an intercept of 0.2 milliseconds (90%CI, −0.87 to 1.26; P = .76).

For the 12-mg dose, the observed geometric mean C_{max} (92 ng/mL) predicted a ΔΔQTcF (or QT effect) of 0.7 milliseconds (90%CI, −0.21 to 1.68). For the 36-mg dose, the observed geometric mean C_{max} (315 ng/mL) predicted a ΔΔQTcF of 2.1 milliseconds (90%CI, 0.91-3.19). Based on this concentration-QTc analysis, a ΔΔQTcF exceeding 10 milliseconds was excluded for deucravacitinib plasma concentrations of at least 500 ng/mL.

Assay Sensitivity

The moxifloxacin concentration-QTc model showed close correspondence to observed values, supporting the proposed model as a reasonable representation between ΔΔQTcF and concentration for moxifloxacin. The relationship between the individual observed moxifloxacin concentrations and ΔΔQTcF is shown in Figure 4. The estimated population slope of the model was 0.0045 milliseconds per ng/mL (90%CI, 0.0034-0.0055; P < .0001) with an intercept of 4.0 milliseconds (90%CI, 2.32-5.64; P = .0001). Assay sensitivity with moxifloxacin was demonstrated with the statistically significant slope and a lower bound of the 2-sided 90%CI of the predicted effect at the observed geometric C_{max} exceeding 5 milliseconds.

Effect on Cardiac Repolarization: QT Interval

The largest least squares (LS) mean ΔΔQTcF with deucravacitinib was 0.8 milliseconds (12-mg dose; 90%CI, −0.9 to 2.5) and 3.0 milliseconds (36-mg dose; 90%CI, 1.3-4.7), both occurring 2 hours after dosing (Figure 5A). The upper bound of the 2-sided 90%CI for ΔΔQTcF values for deucravacitinib was <10 milliseconds at all time points. In contrast, the largest LS mean ΔΔQTcF with the positive control, moxifloxacin, was 12.9 milliseconds (90%CI, 11.2-14.6), at 2 hours after dosing.

The pattern of LS mean ΔQTcF values for deucravacitinib was similar to the pattern for placebo. The largest LS mean ΔQTcF values with deucravacitinib were −1.7 milliseconds (12-mg dose, 3 hours after dosing) and 0.2 milliseconds (36-mg dose, 1 hour after dosing). The LS mean ΔQTcF values for moxifloxacin peaked at 9.2 milliseconds at 3 hours after dosing. No subject had a QTcF of >450 milliseconds or a ΔQTcF of >30 milliseconds at any time point.

Effect on HR and Cardiac Conduction (PR and QRS Intervals)

The LS mean ΔHR values for deucravacitinib, moxifloxacin, and placebo followed a similar diurnal pattern. For deucravacitinib, the largest LS mean ΔHR was 8.2 bpm (12-mg dose; 90%CI, 6.6-9.7) and 8.7 bpm

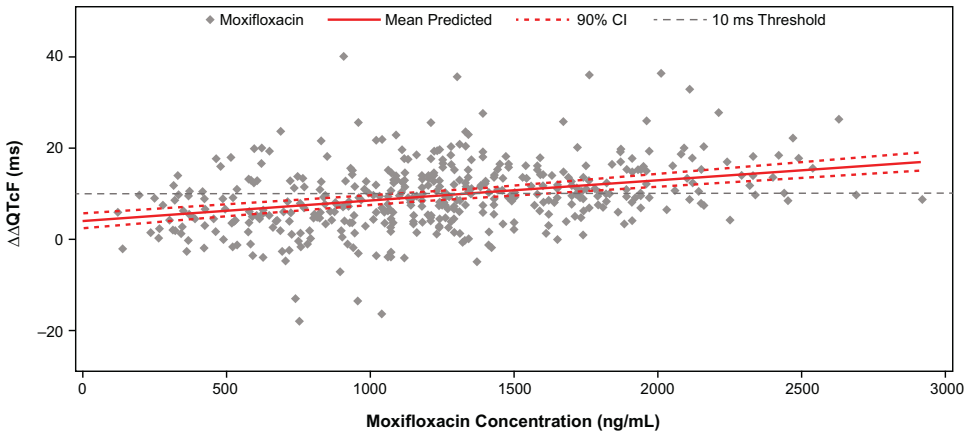

Figure 4. Scatter plot of moxifloxacin concentration versus placebo-corrected change from baseline QTcF interval (ΔΔQTcF). Prediction was based on the model ΔΔQTcF = 3.98 + concentrations of moxifloxacin • 0.0045. The solid red line with dashed red lines denotes the model-predicted mean ΔΔQTcF with 90%CI. The green diamonds denote the pairs of observed moxifloxacin plasma concentrations and observed ΔΔQTcF by subjects for the dose of placebo.

(36-mg dose; 90%CI, 7.2-10.3), both at 6 hours after dosing. Placebo and moxifloxacin also had the largest LS mean ΔHR at 6 hours after dosing (8.9 and 8.7 bpm, respectively). The largest LS mean ΔΔHR for deucravacitinib was 0.6 bpm (12 mg; 90%CI, −0.9 to 2.1) and 4.0 bpm (36 mg; 90%CI, 2.6-5.5), both at 1 hour after dosing (Figure 5B). No outlier values for HR change were observed.

The LS mean ΔPR values for deucravacitinib, moxifloxacin, and placebo were negative at all time points except for 0.5 hours after dosing (0.2 milliseconds for deucravacitinib 12 mg and 36 mg). Values for LS mean ΔΔPR were within ±2.9 milliseconds (Figure 5C). The largest LS mean ΔQRS was 0.2 milliseconds (placebo at 0.5 hours after dosing; moxifloxacin at 0.5, 1, and 1.5 hours after dosing); LS mean ΔQRS values for deucravacitinib 12 mg and 36 mg were ≤0.1 milliseconds at all time points. LS mean ΔΔQRS values varied within ±0.4 milliseconds among all treatments at all time points (Figure 5D). No outlier values for PR or QRS were observed.

Additional ECG Parameters: T-Wave Morphology, U-Wave Presence

Treatment-emergent changes of T-wave morphology were occasionally observed in all treatment periods, including during placebo treatment. The frequencies of flat, notched, and biphasic T-wave morphologies for deucravacitinib and moxifloxacin were lower than or the same as for placebo. No U-wave observations were recorded during the study.

Pharmacokinetics

Deucravacitinib 12 and 36 mg were rapidly absorbed, reaching t_{max} in <3 hours (Table 2; Figure 6). The 3-fold increase in dose from 12 to 36 mg produced a similar magnitude of increase in systemic exposure (3.4-fold increase in geometric mean C_{max} and geometric mean AUC from time 0 extrapolated to infinite time). Moreover, t_{max} and $t_{1/2}$ were similar between the 12- and 36-mg doses. After a single dose of moxifloxacin, plasma concentration increased quickly and reached its maximal value at 2 hours, and remained detectable for 72 hours.

Safety

A total of 35 AEs were recorded in 5 subjects (12.8%) each for placebo and deucravacitinib 12 mg, 8 subjects (20.5%) for deucravacitinib 36 mg, and 8 subjects (20.0%) for moxifloxacin. Of the 25 treatment-related AEs, 17 were related to deucravacitinib (8 AEs in 4 subjects at the 12-mg dose and 9 AEs in 7 subjects at the 36-mg dose), and 4 each were related to moxifloxacin and placebo (in 3 and 4 subjects, respectively).

The most frequently occurring AEs by number and percentage of subjects were constipation for placebo (n = 2 [5.1%]) and headache for deucravacitinib 12 mg (n = 3 [7.7%]), deucravacitinib 36 mg (n = 6 [15.4%]), and moxifloxacin (n = 3 [7.5%]). No deaths occurred, and all AEs resolved by the end of the study. The majority (27/35) of AEs were mild in severity. Five AEs (pharyngitis, lymphadenopathy, cellulitis, and trismus in 1 subject; elevated blood CPK in another subject) were severe and occurred in 2 subjects (5.0%), and 3 AEs (n = 1 each for headache, bilateral otitis externa, and constipation) were moderate. Administration of moxifloxacin was followed by a severe increase in CPK in 1 subject, the only clinically meaningful laboratory abnormality. The elevated CPK was considered unrelated to the study treatment but led to study drug discontinuation; it resolved without intervention. Another subject reported 4 severe AEs, also classified

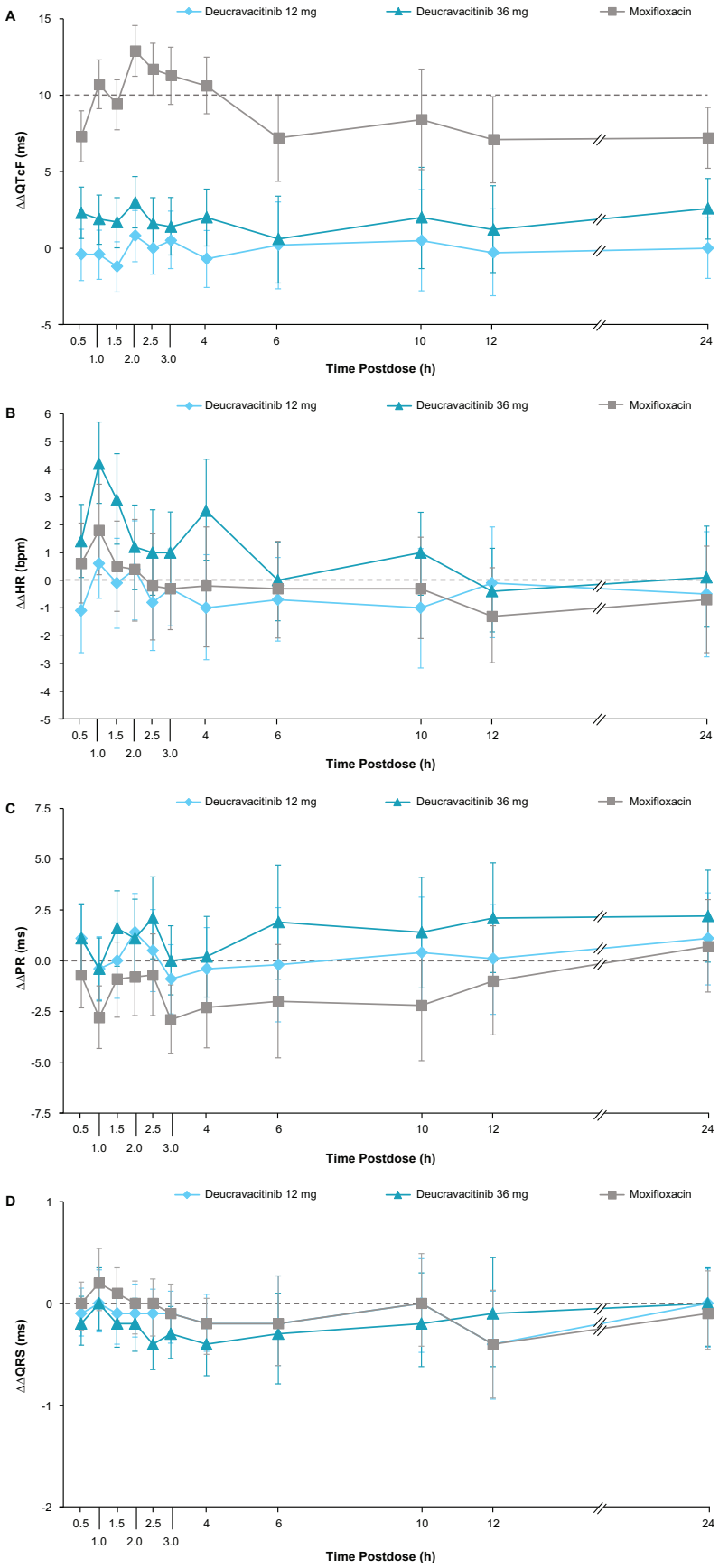
A
Deucravacitinib 12 mg
Deucravacitinib 36 mg
Moxifloxacin
ΔΔQTcF (ms)
Time Postdose (h)
B
Deucravacitinib 12 mg
Deucravacitinib 36 mg
Moxifloxacin
ΔΔHR (bpm)
Time Postdose (h)
C
Deucravacitinib 12 mg
Deucravacitinib 36 mg
Moxifloxacin
ΔΔPR (ms)
Time Postdose (h)
D
Deucravacitinib 12 mg
Deucravacitinib 36 mg
Moxifloxacin
ΔΔQRS (ms)
Time Postdose (h)

Table 2. Plasma Deucravacitinib PK Parameters

Parameter	Deucravacitinib 12 mg (n = 39)	Deucravacitinib 36 mg (n = 39)
C_{max}, ng/mL		
Geometric mean	91.9	315
Arithmetic mean	95.3	324
SD	26.3	81.4
%CV	27.6	25.1
Min, max	51.9, 156	184, 544
t_{max}, h		
Median	2.60	2.10
Min, max	1.10, 4.12	0.600, 4.10
$AUC_{0\text{-}t}$, ng • h/mL		
Geometric mean	892	3060
Arithmetic mean	928	3177
SD	265	899
%CV	28.5	28.3
Min, max	503, 1561	1777, 5300
$AUC_{0\text{-}inf}$, ng • h/mL		
Geometric mean	910	3084
Arithmetic mean	946	3201
SD	268	906
%CV	28.3	28.3
Min, max	511, 1601	1803, 5331
$t_{1/2}$, h		
Arithmetic mean	13.4	13.0
SD	5.92	4.32
Min, max	5.71, 28.0	5.62, 22.5

$AUC_{0\text{–}inf}$, area under the plasma concentration–time curve from time 0 extrapolated to infinity; $AUC_{0\text{-}t}$, area under the plasma concentration–time curve from time 0 to time of last quantifiable concentration; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; PK, pharmacokinetics; $t_{1/2}$, terminal-phase half-life; t_{max}, time of maximum observed plasma concentration.

as serious AEs (SAEs) due to hospitalization, after receiving the fourth and final treatment (deucravacitinib 12 mg): 3 SAEs were considered related to the study drug (severe pharyngitis, lymphadenopathy, cellulitis), and 1 SAE (trismus) was considered unrelated to the study drug. The subject was hospitalized and treated with intravenous and oral antibiotics, dexamethasone, prednisone, and hydrocodone/acetaminophen, and the AEs resolved by the end of the study.

During physical examination, 1 subject had the clinically significant finding of moderate bilateral otitis externa, considered related to the study drug (deucravacitinib 36 mg). The subject was administered acetaminophen and ofloxacin, and the AE resolved by the end of the study.

Discussion

A negative QTc study, as found in the current study, has an upper bound of <10 milliseconds for the 2-sided

Figure 5. Placebo-corrected change (A) from baseline QTcF (ΔΔQTcF), (B) from baseline heart rate (ΔΔHR), (C) from baseline PR interval (ΔΔPR), and (D) from baseline QRS interval (ΔΔQRS) for deucravacitinib and moxifloxacin. Least squares mean and 90%CI based on a linear mixed-effects model: ΔQTcF = period + sequence + time + treatment + time • treatment + baseline QTcF. ΔHR = period + sequence + time + treatment + time • treatment + baseline HR. ΔPR = period + sequence + time + treatment + time • treatment + baseline PR. ΔQRS = period + sequence + time + treatment + time • treatment + baseline QRS. An unstructured covariance structure was used to specify the repeated measures (time for subjects within period). Baseline was defined as the mean of the 4 predose values on days 1, 6, 11, and 16 in each corresponding treatment period. The dotted lines indicate (A) the threshold of 10 ms, (B) the reference line of 0 bpm, (C) the reference line of 0 ms, and (D) the reference line of 0 ms. bpm, beats per minute; QTcF, QT interval corrected for heart rate using the Fridericia method; ΔHR, the individual change from baseline heart rate for placebo recipients calculated at a specific time point; ΔPR, the individual change from baseline PR interval for placebo recipients calculated at a specific time point; ΔQRS, the individual change from baseline QRS interval for placebo recipients calculated at a specific time point; ΔQTcF, the individual change from baseline QTcF for placebo recipients calculated at a specific time point.

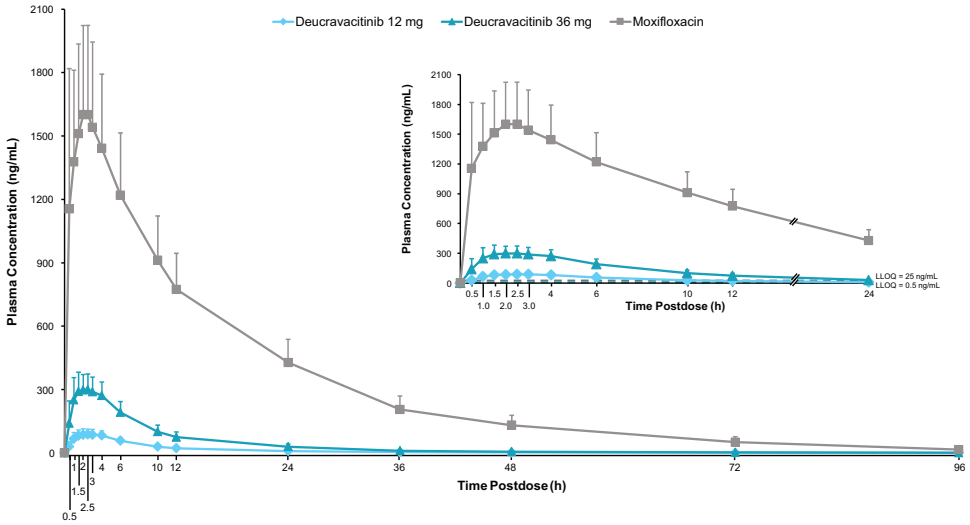

Figure 6. Mean plasma concentration over time for deucravacitinib 12 mg, deucravacitinib 36 mg, and moxifloxacin. The dotted lines indicate lower limit of quantitation (LLOQ) for deucravacitinib and moxifloxacin. The vertical bars indicate standard deviation.

90%CI for QTc effect and indicates that only routine ECG monitoring is necessary to monitor safety in future trials.[14]

Moxifloxacin, a fluoroquinolone antibiotic, is the most commonly used positive control in TQT studies, reproducibly prolonging the QT interval without conferring proarrhythmic risk to study subjects.[15–19] Moxifloxacin is used as a positive control to detect small increases in QTc from baseline when assessing assay sensitivity.[20] In the current study, moxifloxacin was used as the positive control at the standard dose of 400 mg, as has been done in similarly designed TQT studies of other agents (eg, tofacitinib).[21,22] Assay sensitivity was demonstrated by the observation of a QTcF prolongation effect of moxifloxacin: In the current study, the exposure-response relationship for moxifloxacin had a significant slope ($P \leq .1$), and the lower limit of the 90%CI of the predicted ΔΔQTcF at the observed geometric mean C_{max} was >5 milliseconds.[21] In contrast to the QTcF prolongation observed with moxifloxacin, clinically meaningful QTcF prolongation (ie, >10 milliseconds) with deucravacitinib treatment was excluded at clinically relevant and supratherapeutic plasma concentrations of at least 500 ng/mL.

The pattern of ΔQTcF for deucravacitinib followed the pattern for placebo, further suggesting that deucravacitinib has no effect on cardiac repolarization. No subject had QTcF >450 milliseconds, and deucravacitinib did not affect HR or cardiac conduction (PR and QRS intervals). No U-wave presence was observed. Changes in T-wave morphology were occasionally observed in all treatment periods, including placebo, but the absence of clinically meaningful QTc prolongation suggests that T-wave morphology changes do not reflect a proarrhythmogenic propensity of deucravacitinib. Furthermore, the AEs of torsades de pointes and tachyarrhythmia have not been reported in clinical trials of deucravacitinib to date.[9,10] Changes from baseline in blood pressure and HR were similar and not clinically meaningful across all deucravacitinib treatments.

Overall, deucravacitinib was generally well tolerated. The majority of AEs were mild in severity, and all AEs resolved by the end of the study. Headache was the most common AE (8 subjects). Three treatment-related SAEs (pharyngitis, cellulitis, and lymphadenopathy) were reported in 1 subject following administration of the last treatment (deucravacitinib 12 mg). The SAEs resolved by the end of the study with appropriate treatment and did not lead to discontinuation.

A phase 1, randomized crossover study in healthy adults tested single deucravacitinib doses of up to 40 mg and multiple doses of up to 12 mg twice daily to monitor for potential cardiovascular and ECG effects (NCT02534636). Deucravacitinib did not have an effect on HR, and no subject had arrhythmia or clinically relevant changes in supine, sitting, or standing systolic blood pressure or diastolic blood pressure. No clinically significant ECG findings were observed during the dosing or follow-up period.

The safety and efficacy of deucravacitinib 6 mg and 12 mg once daily are being evaluated in a phase 2 trial in patients with active psoriatic arthritis.[10] Additionally, deucravacitinib is being evaluated in phase 2 trials in systemic lupus erythematosus (NCT03920267 and NCT03252587), lupus nephritis (NCT03943147), Crohn disease (NCT03599622), and ulcerative colitis (NCT03934216 and NCT04613518). Deucravacitinib 6 mg once daily is also being administered in phase 3 trials in patients with moderate to severe psoriasis (NCT03924427, NCT04036435, NCT03624127,[23]

NCT04167462, and NCT03611751). A supratherapeutic deucravacitinib dose of 36 mg did not affect ECG parameters in this study, suggesting that the dose range being used in clinical trials in psoriasis and other therapy areas would not be expected to affect ECG parameters.

Conclusion

Deucravacitinib given as a single oral therapeutic dose of 12 mg or a supratherapeutic dose of 36 mg does not have clinically relevant effects on ECG parameters, including QTcF interval, HR, PR interval, and QRS interval. These results indicate that the current study met the International Conference on Harmonization E14–specified criteria for a negative TQT study. Overall, deucravacitinib was generally well tolerated, consistent with previous safety findings in other clinical trials with deucravacitinib.

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Conflicts of Interest

The authors are employees of and shareholders in Bristol Myers Squibb.

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