Evaluation of the Effect of Selumetinib on Cardiac Repolarization: A Randomized, Placebo- and Positive-Controlled Crossover QT/QTc Study in Healthy Subjects

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ABSTRACT

Purpose: Selumetinib (AZD6244, ARRY-142886) is an oral, potent, and selective allosteric mitogen-activated protein kinase 1/2 inhibitor with a short t1/2. The purpose of this study was to characterize the effect of selumetinib on cardiac repolarization and a potential exposure–QT effect relationship.

Methods: A double-blind (selumetinib), randomized, 3-period crossover study was conducted to assess the effects of a single oral dose of selumetinib (75 mg) on the QTc interval compared with placebo, using moxifloxacin as an open-label positive control, in healthy male subjects aged 18 to 45 years. QT intervals were evaluated by using the Fridericia formula (QTcF) and the Bazett formula. Further analysis was conducted by using nonlinear mixed effects modeling to characterize any relationship between selumetinib exposure and QTc and was used to predict the effect if selumetinib 150 mg was administered. All adverse events were characterized and recorded.

Findings: A total of 54 healthy male subjects were enrolled, and 48 completed all treatments. Mean age was 27 years; four subjects were of Hispanic or Latino ethnicity, and 53.7% were White and 46.3% were Black. The BMI of subjects ranged from 19.4 to 29.6 kg/m². After a single oral dose of selumetinib 75 mg, the highest upper bound of the 2-sided 90% CI for placebo-corrected, baseline-adjusted QTcF (ΔΔQTcF) over the 24-hour postdose measurement interval was 2.5 milliseconds, which was well below the 10-millisecond upper bound for concluding no effect. The relationship between ΔΔQTcF and selumetinib concentrations was adequately described by using a nonlinear mixed effect model. The mean estimated ΔΔQTcF interval prolongation based on the geometric mean Cmax of 75 mg selumetinib was 2.38 milliseconds (90% CI, 1.25 to 3.52), which was in good agreement with the statistical analysis results. The model also predicted mean ΔΔQTcF interval prolongations of 4.70 milliseconds (90% CI, 2.46 to 6.95) after a single supratherapeutic dose of selumetinib 150 mg, indicating the upper bound of 2-sided 90% CIs for ΔΔQTcF are predicted to be <10 milliseconds. Selumetinib, administered as a single 75 mg oral dose, was generally safe and well tolerated.

Implications: Selumetinib 75 mg did not cause any QT/QTc interval prolongation in these healthy subjects, and selumetinib is not expected to have a clinically relevant effect on cardiac repolarization in patients at the anticipated therapeutic dose of 75 mg. The model also demonstrated the low potential for any QTc effects of selumetinib at doses higher than the standard therapeutic dose.

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INTRODUCTION
Selumetinib (AZD6244, ARRY-142886) is an oral, potent, and selective allosteric inhibitor of mitogen-activated protein kinase (MEK)1/2. MEK is a critical enzyme in the RAS/RAF/MEK/ERK pathway that regulates key cellular activities, including proliferation, survival, and cell cycle regulation. Selumetinib has shown the ability to block cell proliferation in vitro, regardless of sensitivity to conventional chemotherapy. It also effectively inhibited ERK phosphorylation and suppressed proliferation in vivo in human melanoma–bearing nude mice. In addition, selumetinib inhibited acquisition of the breast cancer stem cell phenotype and prevented lung metastasis of triple-negative breast cancer in a xenograft model. Selumetinib is under clinical development in a variety of indications, including differentiated thyroid cancer (NCT01843062) and neurofibromatosis type 1 (NCT01362803). The pharmacokinetic (PK) profile of selumetinib has been studied in patients with various tumors. It has a short t½ (mean, 5.33 hours), and its PK profile is approximately dose proportional from 25 mg up to 150 mg in patients with advanced cancer. The N-desmethyl metabolite circulates at <10% of selumetinib in plasma. In cloned human ether-a-go-go–related gene channels expressed in mammalian cells, selumetinib produced no significant effects at up to the maximum test concentration (Investigator’s Brochure, Project Code D1532000000, 30 March 2015, AstraZeneca, UK), which is ~700- to 1000-fold greater than the half maximal inhibitory concentration for inhibition of the activity of isolated MEK in enzyme assays. In addition, N-desmethyl selumetinib produced no significant effects on the human ether-a-go-go–related gene current at up to the maximum test concentration, ~10-fold higher than that was tested for selumetinib (Investigator’s Brochure, Project Code D1532000000, 30 March 2015, AstraZeneca, UK). However, it is important to understand—and it is a regulatory expectation to characterize—any risk that new medicines prolong cardiac repolarization to identify any potential clinical consequences such as torsade de pointes. Many drugs in a range of indications do prolong the QTc interval, and some have been found to have clinical consequences. This outcome is particularly important in the oncology setting in which a number of existing drugs have been shown to prolong the QTc interval.

The design of QT studies has been optimized in recent times and usually contains a positive control agent (eg, moxifloxacin) and time-matched QTc readings after dosing with placebo. In addition, the end points and sizing of the studies have become standardized. The primary objective of the present study was to assess the effect of a single dose of selumetinib (75 mg) on the change in time-matched QT intervals evaluated by using the Fridericia formula (QTcF) compared with placebo. In addition, the safety, tolerability, and PK parameters of selumetinib and its N-desmethyl metabolite were examined. In support of the primary statistical analysis, an exposure–response analysis between selumetinib concentrations and the placebo-corrected, baseline-adjusted mean QTcF (ΔΔQTcF) was conducted.

PATIENTS AND METHODS
Study Design
The study was conducted between March 2014 (first subject enrolled) and August 2014 (last subject’s last visit), and the clinical study protocol was approved by the MidLands Institutional Review Board (Overland Park, Kansas). The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation/Good Clinical Practice and applicable regulatory requirements, as well as the AstraZeneca policy on bioethics. Written informed consent was obtained from all healthy subjects before initiation of the study. This was a double-blind (selumetinib), placebo-controlled, open-label (moxifloxacin), positive-controlled, randomized, 3-period crossover study to assess the effects of a single oral dose of selumetinib (75 mg) on QTc interval compared with placebo; moxifloxacin 400 mg was used as a positive control. Moxifloxacin was administered in an open-label fashion due to its clear clinical signal of QT prolongation and consistent PK profile, and because at a 400 mg dose, it has no clinically significant risk to exposed healthy volunteers.
A previous clinical study in patients established 75 mg BID of selumetinib as the maximum tolerated dose, based on 2 dose-limiting toxicities in the 100 mg BID dose cohort of grade 3 dermatitis acneiform and grade 3 pleural effusion. The dose of selumetinib 75 mg was considered to be within the therapeutic dose range and was the maximum dose permitted in healthy volunteers. A BID dose of selumetinib 75 mg has been investigated in other efficacy studies, and minimal accumulation of selumetinib was observed after BID dosing for 8 days. Because a single dose of selumetinib 75 mg was considered the highest acceptable dose to be administered in healthy volunteers, this study did not include a supratherapeutic dose. Phase III trials of selumetinib used a dose of 75 mg BID.

Study subjects were healthy, nonsmoking men aged 18 to 45 years with a body mass index between 18 and 30 kg/m² and weight between 50 and 100 kg. Subjects were to use barrier methods of contraception, unless their partners were postmenopausal, surgically sterile, or were using accepted contraceptive methods. Key exclusion criteria were as follows: clinically significant disease or disorder; clinically important abnormalities in the rhythm, conduction, or morphology on a resting ECG recording; history of additional risk factors for torsade de pointes; abnormal vital signs; use of any prescribed medicine and over-the-counter drugs within 2 weeks of administration of the investigational product; and excessive intake of caffeine-containing drinks or food.

Subjects were screened within 28 days before randomization. During each 3-day treatment period, each subject received the following on 1 occasion: selumetinib (blinded), placebo (blinded; capsules matched those of selumetinib), and moxifloxacin (open-label). The order in which the drugs were administered was determined by randomization. The randomization scheme was produced by Quintiles (Overland Park, Kansas) by using the AstraZeneca Global Randomization system (GRand), applying a 3-period, 3-treatment, Williams Latin square design. Randomization codes were assigned strictly sequentially as subjects became eligible for randomization.

Each administration was separated by a washout period of at least 3 days. Subjects underwent an 8-hour fast before dosing, and no food intake was allowed until 4 hours after dosing. The subjects were allowed no fluid intake from 1 hour before the investigational product administration until 1 hour after, except for the water needed to swallow the investigational product.

**Pharmacodynamic Measurements**

Twelve-lead continuous digital ECG (dECG) recordings were obtained by using Schiller Cardiovit CS-200 ECG recorders (Schiller AG, Baar, Switzerland). The analyses of all dECGs were performed at the AstraZeneca ECG Centre (AstraZeneca ECG Core Lab, Gothenburg, Sweden) in fully blinded mode (ie, blinded to sequence, treatment, time and subject identifier). The waveform analysis was performed by using the EClysis System (ECG Analysis, AstraZeneca proprietary tool, Gothenburg, Sweden), a software tool for automated dECG waveform reading, annotation, and interval calculation that also allows manual adjudication (ie, a semi-automated analysis).

No clinically meaningful effects induced by selumetinib or N-desmethyl selumetinib on heart rate (HR) have been observed in previous studies. Continuous 12-lead dECG recordings were captured for 20 minutes predose at baseline and for 5 minutes at time points 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose. All dECG recordings were obtained after at least 10 minutes of supine rest at all time points and just before supine vital signs and blood sample collection for PK assessments. For QTcF measurements, the precordial lead V2 was used as the primary lead; precordial lead V5 was used as the backup lead for all time points when lead V2 was found to be unsuitable for analysis and evaluation. The QT interval was measured (in milliseconds) from the onset of the QRS complex to the end of the T wave, which was determined by use of a tangent on the T-wave down slope and the intercept with the iso-electric line. Using EClysis software, the tangent was derived between the 20% and 80% repolarization points on the T wave calculated from the top of the T wave to the iso-electric line.

The dECG-collected or -derived variables were as follows: the QT interval (measured from the onset of the QRS-complex to the end of the T wave); the QTcF in milliseconds; HR in beats per minute; the RR interval (the time between corresponding points on 2 consecutive R waves in seconds); the PR interval (measured from the onset of the P wave to the onset of the QRS complex in milliseconds); the QRS duration (the interval measured from the onset of the QRS...
complex to the J point in milliseconds); and the QT interval corrected for HR by using the Bazett formula (QTcB) in milliseconds. Ten-second dECG replicates were extracted every 30 seconds from the predefined 5- or 20-minute continuous recordings. The extracted data were averaged to arrive at a mean value for each time point. The QT interval was corrected for RR interval to obtain QTc variables. The general formula for QTc was QT/RR\(^{b}\), with QT intervals expressed in milliseconds and the RR interval in seconds. The formula for QTcF was \(b = 1/3\), \(b = 1/2\). \(12\)

PK Assessments

Plasma PK samples were collected for selumetinib, N-desmethyl selumetinib, and moxifloxacin at predose and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 12.0, 24.0, and 48.0 hours postdose to capture the PK profile of these drugs. Covance Laboratories, Inc (Madison, Wisconsin), performed the analysis of plasma samples for selumetinib, N-desmethyl selumetinib, and moxifloxacin concentrations as part of the AstraZeneca–Covance Clinical Bioanalysis Alliance. Sensitive LC-MS/MS assays were developed and validated that demonstrated acceptable precision, accuracy, and selectivity for selumetinib and its metabolites in the appropriate matrices. \(19\) They were validated based on guidance from the US Food and Drug Administration and the European Medicines Agency \(20\)-\(22\) and on standard laboratory operating procedures. To demonstrate acceptable in-study performance, incurred sample reproducibility experiments were also performed.

Selumetinib and N-desmethyl selumetinib were extracted from human plasma treated with \(K_2\)EDTA anticoagulant by protein precipitation and analyzed by using liquid chromatography with a Sciex API (AB Sciex LLC, MA, USA) 5000 or 5500 triple/quad tandem mass spectrometer. The method used stable label carbon-13 internal standards and was validated over the range of 2 to 2000 ng/mL for selumetinib, and 2 to 500 ng/mL for N-desmethyl selumetinib. The ability to dilute overrange samples was also confirmed.

Moxifloxacin was extracted from human plasma treated with \(K_2\)EDTA anticoagulant by protein precipitation and analyzed by using liquid chromatography with a Sciex API 4000 tandem mass spectrometer. The method uses a stable label deuterated internal standard and was validated over the range of 2.5 to 5000 ng/mL for moxifloxacin. AUC\(_{0-t}\), \(C_{\text{max}}\), and \(T_{\text{max}}\) were calculated for selumetinib, N-desmethyl selumetinib, and moxifloxacin.

Study End Points

The primary end point in this study was the effect of a single dose of selumetinib (75 mg) on the change in time-matched QTcF interval compared with placebo. Secondary end points included: the effect of selumetinib on QRS, QT, HR, RR, PR, and QTcB; mean changes in time-matched QTcF interval after moxifloxacin administration compared with placebo; PK examination of selumetinib, N-desmethyl selumetinib, and moxifloxacin; the relationship between plasma concentration and cardiac ventricular repolarization effect on the heart after a single oral dose of selumetinib or moxifloxacin by assessments of plasma concentrations of selumetinib, moxifloxacin, and the QT/QTcF interval on dECGs; and assessment of the safety and tolerability of selumetinib.

Statistical Analysis

Assuming a 3-millisecond effect of selumetinib on QTcF, an 8.5-millisecond residual variability, and 10 postdose ECG assessments, 47 evaluable subjects were needed to provide > 90% power to conclude no effect on QTcF at or above the 10-millisecond threshold; to allow for discontinuations, 54 healthy subjects were randomized to study. The safety analysis set included all subjects who received at least 1 dose of treatment (selumetinib, placebo, or moxifloxacin). The PK analysis set included all subjects who received at least 1 dose of selumetinib or moxifloxacin and had at least 1 postdose PK measurement with no important events or protocol deviations thought to significantly affect the PK parameters of the drug.

The pharmacodynamic (PD) analysis set included all subjects who received at least 1 dose of treatment (selumetinib, placebo, or moxifloxacin) and had at least 1 postdose QT measurement with no important events or protocol deviations thought to significantly affect the QT. The primary analysis of change from baseline for QTcF was conducted by using a repeated measures linear mixed model with fixed effects for treatment, period, time, period-by-time interaction, treatment-by-time interaction, and the baseline value (predose from each period) as a covariate. Subjects were treated as a random effect, and time was treated as a repeated effect, within a subject period, using a first-order autoregressive covariance structure. At each
of the postdose ECG nominal times, the least-squares means with corresponding 2-sided 90% CIs for selumetinib compared with placebo were calculated; the upper CI bounds needed to be <10 milliseconds to conclude no effect on the QTcF interval.

In addition, a sensitivity analysis was performed in which the treatment comparison (selumetinib vs placebo) was performed at each time point, using an ANCOVA model with subject as a random effect, period and treatment as fixed effects, and baseline QTcF (predose from each period) as a covariate. The same statistical model as described for the primary analysis of QTcF was used to assess the effect of treatment for change from baseline of QTcB, QT, HR, RR, QRS, and PR.

To assess the assay sensitivity of the study, the treatment effect of moxifloxacin (from the aforementioned model) was evaluated by estimating the mean difference from placebo for the mean of QTcF during the 1- to 4-hour interval postdose with a corresponding 2-sided 90% CI. The lower bound of this 2-sided interval was required to be >5 milliseconds to establish assay sensitivity.

### Concentration-QTc Effect Modeling

A population concentration-effect model describing the relationship between selumetinib concentrations and the baseline-subtracted, placebo-corrected QTc (∆∆QTcF) was established by using a nonlinear mixed effects modeling approach with NONMEM version 7.3 (ICON, Hanover, Maryland) and the first-order conditional estimation method with interaction. Linear or E_{\text{max}}-type of nonlinear relationships of ∆∆QTcF versus selumetinib concentrations was examined. Models were progressed by using the Akaike information criterion \(^{24}\) as ∆OFV + 2∆df, where ∆OFV and ∆df are the difference in the objective function value (OFV) of NONMEM and the difference in number of model parameters between the competitive model and the reference model (degree of freedom).

The predictive performance of the final ∆∆QTcF–concentration model was assessed with a visual predictive check. Simulation of 1000 new datasets was conducted by using the final model with the estimated fixed effects and random effects model parameters. The ∆∆QTcF-concentration profiles were plotted for the 50th percentile and the 5th and 95th percentiles (presenting the 90% prediction interval) of the simulated data and overlaid with observed data. Nonparametric bootstrapping (1000 replicates) was also conducted, and empirical 95% CIs were constructed by obtaining the 2.5th and 97.5th percentiles of the resulting parameter distributions for those bootstrap runs with successful convergence. The final model parameter estimates were compared with the bootstrap median parameter estimates to evaluate the final model performance.

The potential ∆∆QTcF prolongation for anticipated selumetinib therapeutic dose (75 mg) was evaluated at geometric mean C_{\text{max}} of selumetinib with the upper bound of the 2-sided 90% CI of the population mean estimate of the slope. \(^{25}\) In addition, the model was also applied to predict the potential ∆∆QTcF prolongation if a higher dose is administered. The geometric mean C_{\text{max}} of selumetinib observed in patients with advanced solid tumors after a single dose of 150 mg selumetinib was used. \(^{9}\)

### Tolerability Assessment

Vital sign measurements, physical examinations, and safety laboratory analyses involving routine hematology, serum chemistry, and urinalysis were obtained and reviewed by the investigator during the study and at a follow-up examination. All adverse events (AEs) were evaluated by the investigator and characterized with respect to intensity, duration, relationship to study drug, and outcome.

### RESULTS

#### Subject Demographic Characteristics

A total of 54 healthy subjects were randomized to treatment. Forty-eight subjects completed the treatments, and 47 completed the study: 3 subjects were lost to follow-up; 2 were withdrawn due to protocol deviations; and 2 withdrew consent. Subject disposition is described in Figure 1. All subjects were male, with a mean age of 27 years (range, 18–45 years). Four subjects were of Hispanic or Latino ethnicity, and there was approximately equal distribution between white (53.7%) and black (46.3%) subjects. The body mass index of subjects ranged from 19.4 to 29.6 kg/m\(^2\).

#### PD Profile

A total of 50 subjects treated with selumetinib or moxifloxacin and 49 subjects treated with placebo were available for QTc interval analysis. The ∆∆QTcF for selumetinib 75 mg was <5 milliseconds.
at each time point, and all upper limits of the 2-sided 90% CI were well below 10 milliseconds (Figure 2). The highest upper bound of the 2-sided 90% CIs for ΔΔQTcF over the 24-hour postdose measurement interval was 2.5 milliseconds at 1.5 hours after dosing. Similar results were obtained from the sensitivity analysis, with the highest upper bound of the 2-sided 90% CIs for ΔΔQTcF at 2.3 milliseconds. Similar findings were observed by using QTcB; the highest upper bound of the 2-sided 90% CIs for ΔΔQTcB over the 24-hour postdose measurement interval was 3.2 milliseconds.

After a single oral dose of moxifloxacin 400 mg, the largest ΔΔQTcF increase of 11.9 milliseconds (95% CI, 10.3 to 13.6) was observed 3 hours after dosing. Assay sensitivity was demonstrated by comparing moxifloxacin and placebo QTcF averaged over the 1- to 4-hour range postdose, using the mixed effects ANCOVA model. The lower bound of the 2-sided 90% CI for mean ΔΔQTcF over the 1- to 4-hour time interval postdose was >5 milliseconds (ie, 9.4 milliseconds), thereby establishing assay sensitivity.

Changes from baseline to the observed maximum in QTcF or QTcB did not exceed 30 milliseconds at any time point over the 24-hour period after dosing with selumetinib 75 mg or placebo. There were no subjects with absolute QTcF or QTcB values >450 milliseconds.

There were no HR events for selumetinib or placebo that met the predefined criterion of >100 beats/min. Three subjects receiving selumetinib treatment and 1 subject taking placebo had a PR interval >200 milliseconds. All of these subjects who had a QRS interval >110 milliseconds with treatment had a QRS interval >110 milliseconds at baseline, as well as at predose for some subjects. Therefore, none of these PR or QRS events was considered clinically significant by the principal investigator.
PK Profile

The PK profiles showed that selumetinib was rapidly absorbed after oral administration; median $T_{\text{max}}$ for selumetinib and N-desmethyl selumetinib occurred at 1 hour postdose (Table I). The geometric mean metabolite-to-parent ratios for $\text{AUC}_{0-\infty}$ and $C_{\text{max}}$ were 0.0802 and 0.0733, respectively. The arithmetic mean apparent clearance was 19.0 L/h, which is close to the reported average value of 16.0 L/h with a range of 7.77 to 33.3 L/h. The arithmetic mean $V_{ss/F}$ was 145 L, which is also similar to the reported average value of 106.7 L with range of 52.3 to 219 L. The geometric mean $\text{AUC}_{0-t}$ and $C_{\text{max}}$ for moxifloxacin was 22,700 ng h/mL and 1690 ng/mL, respectively, after administration of moxifloxacin 400 mg. The PK parameters of moxifloxacin observed in this study were similar to those in the published literature.

**PK/PD Analysis**

The $\Delta \Delta \text{QTcF}$ dataset included 47 subjects with 468 observations with the range of selumetinib concentration between 2.41 and 2325.14 ng/mL. The relationship between selumetinib concentration and $\Delta \Delta \text{QTcF}$ was tested by using linear function and nonlinear $E_{\text{max}}$-type function. Random effects (IIV) were tested on the intercept, slope, maximum $\Delta \Delta \text{QTcF}$ interval prolongation ($E_{\text{max}}$), or half maximal effective concentration ($EC_{50}$). The linear model with IIV on intercept was the best model to describe the selumetinib concentration and $\Delta \Delta \text{QTcF}$ relationship. The final model parameter estimates and bootstrap results are presented in Table II.

The parameter of interest in the model was the coefficient for the concentration effect (slope of a linear model), which represents the effect of the drug on $\Delta \Delta \text{QTcF}$. The 95% CI for the slope parameter did not include 0, indicating that the data support a prolongation of the QTcF interval. All model parameters were

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**Table I. Summary statistics of selumetinib, N-desmethyl-selumetinib, and moxifloxacin pharmacokinetic parameters. Values are given as geometric mean (%CV) for $C_{\text{max}}$ and AUC and as arithmetic mean (SD) for $t_{1/2}$, CL/F, and $V_{ss/F}$.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Selumetinib (n = 50)</th>
<th>N-desmethyl-selumetinib (n = 50)</th>
<th>Moxifloxacin (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AUC}_{0-t}$, ng · h/mL</td>
<td>3980 (24.6)*</td>
<td>285 (29.3)</td>
<td>22,700 (20.3)</td>
</tr>
<tr>
<td>$C_{\text{max}}$, ng/mL</td>
<td>1240 (33.1)†</td>
<td>90.4 (38.3)</td>
<td>1690 (29.5)</td>
</tr>
<tr>
<td>$T_{\text{max}}$, median (minimum-maximum), h</td>
<td>1.02 (0.5-2.5)</td>
<td>1.02 (0.5-3.0)</td>
<td>1.53 (0.5-4.0)</td>
</tr>
<tr>
<td>$t_{1/2}$, h</td>
<td>9.18 (2.64)</td>
<td>8.18 (2.77)</td>
<td>13.1 (2.08)</td>
</tr>
<tr>
<td>CL/F, L/h</td>
<td>19.0 (4.66)</td>
<td>NA</td>
<td>16.5 (3.55)</td>
</tr>
<tr>
<td>$V_{ss/F}$, L</td>
<td>145 (46.5)</td>
<td>NA</td>
<td>303 (53.3)</td>
</tr>
</tbody>
</table>

*NA = not applicable; $V_{ss/F}$ = apparent volume of distribution at equilibrium.

* $n = 49$.

† One ng/mL equals 2.18 nM of selumetinib.
well estimated with good precision (small relative SE), except for the intercept parameter $\theta_1$. The intercept parameter was expected to be 0 on average and could not be well estimated because it represents a drug-unrelated random effect due to baseline and placebo subtraction by definition. The estimate of the intercept from the final model was $-1.16$, and the 95% CI estimated from the bootstrap ($-3.10$ to $1.11$) included 0, which agrees with the interpretation of the intercept parameter.

The predictive performance of the final population PK/PD model was assessed by using a visual predictive check. Overlay plots of the $\Delta\Delta$QTcF versus observed selumetinib concentration with the 95% prediction interval of the simulated data indicated that data simulated from the final model were consistent with the observed data (Figure 3).

In the selumetinib QT study, the geometric mean $C_{\text{max}}$ of selumetinib at a single 75 mg dose was 1240 ng/mL. Therefore, the mean estimated $\Delta\Delta$QTcF interval prolongation was 2.38 milliseconds (90% CI, 1.25 to 3.52). The predicted mean and upper bound of 2-sided 90% CIs for $\Delta\Delta$QTcF were <5 milliseconds at this dose, which is in agreement with the statistical analysis results. The model also predicted mean estimated $\Delta\Delta$QTcF interval prolongations of 4.70 milliseconds (90% CI, 2.46 to 6.95) by using the observed geometric mean $C_{\text{max}}$ of 2447 ng/mL after a single dose of 150 mg selumetinib in patients with advanced solid tumors. The predicted upper bound of 2-sided 90% CIs for $\Delta\Delta$QTcF was <10 milliseconds at this dose, which is double the anticipated Phase III dose. Of note, the $C_{\text{max}}$ observed in the patient study using 150 mg selumetinib was approximately twice that observed in the current 75 mg selumetinib study and thus is supportive of dose-exposure linearity at these doses.

**Tolerability**

There were no deaths or AEs resulting in discontinuation of selumetinib, moxifloxacin, or placebo for any subject. There were no serious AEs in subjects during selumetinib or moxifloxacin treatment and 1 serious, noncausally related AE (hemorrhoids) during placebo treatment. Overall, the percentage of subjects who reported at least 1 AE was similar across all 3 study groups (selumetinib, 9.8%; moxifloxacin, 9.8%; and placebo, 10%). The number (%) of subjects who had at least 1 AE according to System Organ Class is listed in Table III. Headache was the most commonly reported AE in all 3 study arms. All nonserious AEs were of mild intensity and considered unrelated to the investigational product by the principal investigator. There were no clinically relevant abnormal laboratory variables, physical examination, and/or vital signs findings throughout the study.

**DISCUSSION**

This randomized, placebo- and positive-controlled crossover QTc study assessed a single 75 mg dose of selumetinib in healthy subjects. The results indicate that selumetinib had no clinically significant effect on the QT/QTcF interval at this therapeutic dose. Specifically, the highest upper bound of the 2-sided 90% CIs for the placebo-corrected $\Delta\Delta$QTcF value over the 24-hour postdose measurement interval was 2.5 milliseconds, which is well below the 10-millisecond protocol-defined upper bound 90% CI value for regulatory concern.

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**Table II. Final model parameter estimates and bootstrap results.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Population Estimate</th>
<th>RSE, %</th>
<th>Median</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\theta_1$ - intercept</td>
<td>$-1.16$</td>
<td>95</td>
<td>$-1.12$</td>
<td>$-3.10$ to $1.11$</td>
</tr>
<tr>
<td>$\theta_2$ - slope (nM$^{-1}$)</td>
<td>0.00088</td>
<td>29</td>
<td>0.000907</td>
<td>0.000426 to 0.001446</td>
</tr>
<tr>
<td>IIV ($\omega$) intercept</td>
<td>7.3</td>
<td>36</td>
<td>7.0</td>
<td>4.67 to 9.57</td>
</tr>
<tr>
<td>Residual error additive</td>
<td>5.1</td>
<td>11</td>
<td>4.6</td>
<td>4.50 to 5.61</td>
</tr>
</tbody>
</table>

IIV = interindividual variability; RSE = relative standard error.
In addition, there were no absolute QTc interval increases >30 milliseconds from baseline with selumetinib treatment. In contrast, the positive control, moxifloxacin, lengthened the QTc interval, with the largest ΔΔQTcF increase of 11.9 milliseconds and a lower bound of >5 milliseconds (9.4 milliseconds) for the 2-sided 90% CI for mean ΔΔQTcF over the 1- to 4-hour time interval postdose, thus demonstrating assay sensitivity of the study. There were no additional clinically significant effects of either selumetinib or moxifloxacin on the PR or QRS intervals.

The relationship between selumetinib concentration and ΔΔQTcF was adequately described by using a nonlinear mixed effect PK/PD model. The mean estimated ΔΔQTcF interval prolongations based on the geometric mean $C_{max}$ of 75 mg (2.38 milliseconds [90% CI, 1.25 to 3.52]) was in agreement with the primary statistical analysis result, providing further evidence that selumetinib does not have an effect on QTc. In addition, the PK/PD model also predicted mean ΔΔQTcF interval prolongations of 4.70 milliseconds (90% CI, 2.46 to 6.95) after a single dose of selumetinib 150 mg in patients. Overall, selumetinib was well tolerated in this study, with no HR events that met predefined criterion.

Consistent with our study, clinical trials involving other MEK inhibitors (eg, trametinib, binimetinib, PD-0325901) do not report prolongation of QT interval as a concern. For example, in a Phase I study investigating trametinib in patients with solid tumors or lymphoma, an exposure–response analysis was conducted to examine the relationship between plasma concentrations of trametinib and QTc interval. The predicted upper limit of the 90% CI change in QTcP (QTc corrected for HR by using a population factor) after a 2 mg dose of trametinib was 4.0 milliseconds (median, 2.2 milliseconds), indicating no effect of trametinib on QT interval. In addition, in a Phase Ib/II study of binimetinib in combination with LEE011 (an oral CDK4/6 inhibitor) in patients with advanced NRAS-mutant melanoma, no clinically significant QTcF prolongation was reported.

The design of the present study followed established guidelines for the clinical evaluation of QT/QTc interval and included a positive control group, a placebo control group, appropriate blinding, and randomization in healthy subjects. It is generally believed that a QT-prolonging effect can be demonstrated in healthy subjects if a drug has such an effect in patients. In addition, the PK profile of a single dose of selumetinib in this study was similar to that in other healthy subjects and patient studies with selumetinib. Previous studies have shown that the PK profile of selumetinib is broadly similar between patients and healthy subjects, although larger variability was observed in patient studies and, therefore, our findings should be applicable to patients.
The effect of a supratherapeutic dose of selumetinib on cardiac ventricular repolarization could not be explored in this study, as the maximum safety limit set by AstraZeneca is 75 mg as a single dose; the maximum tolerated dose in patients was also considered to be 75 mg. However, the PK/PD model in the present analysis established that the upper bound of the 2-sided 90% CI for $\Delta\Delta$QTcF was $<10$ milliseconds for a 150 mg single dose, which is double that of the Phase III dose, demonstrating the low potential for any QTc effects of selumetinib at doses higher than the standard therapeutic dose. Furthermore, because minimal accumulation in Cmax has been observed with repeat dosing, selumetinib at the proposed therapeutic dose of 75 mg BID is unlikely to have a clinically relevant effect on cardiac repolarization in patients.

Finally, selumetinib and N-desmethyl selumetinib are metabolized by cytochrome P450 (CYP) 1A2, CYP2C19, and CYP3A4 enzymes, with CYP1A2 being primarily responsible for the formation of the N-desmethyl metabolite in vitro in human liver microsomes (unpublished data, in vitro selumetinib metabolism studies). Coadministration of selumetinib with the potent CYP3A4 inhibitor itraconazole or the potent CYP2C19 inhibitor fluconazole increases selumetinib exposure by $\sim 50\%$. Caution may therefore be required when coadministering selumetinib with these

<table>
<thead>
<tr>
<th>System Organ Class/Preferred Term</th>
<th>No. (%) of Subjects</th>
<th>Selumetinib</th>
<th>Moxifloxacin</th>
<th>Placebo</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any AE</td>
<td>5 (9.8)</td>
<td>5 (9.8)</td>
<td>5 (10.0)</td>
<td>13 (24.1)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>0</td>
<td>3 (5.9)</td>
<td>1 (2.0)</td>
<td>4 (7.4)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>1 (2.0)</td>
<td>0</td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0</td>
<td>1 (2.0)</td>
<td>0</td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>0</td>
<td>0</td>
<td>1 (2.0)</td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Rectal hemorrhage</td>
<td>0</td>
<td>1 (2.0)</td>
<td>0</td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>0</td>
<td>0</td>
<td>1 (2.0)</td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>0</td>
<td>0</td>
<td>1 (2.0)</td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>0</td>
<td>1 (2.0)</td>
<td>2 (4.0)</td>
<td>3 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0</td>
<td>0</td>
<td>1 (2.0)</td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
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<td>0</td>
<td>1 (2.0)</td>
<td>1 (1.9)</td>
<td></td>
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<tr>
<td>Pain in extremity</td>
<td>0</td>
<td>1 (2.0)</td>
<td>0</td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>3 (5.9)</td>
<td>2 (3.9)</td>
<td>0</td>
<td>5 (9.3)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>3 (5.9)</td>
<td>1 (2.0)</td>
<td>0</td>
<td>4 (7.4)</td>
<td></td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>0</td>
<td>1 (2.0)</td>
<td>0</td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>1 (2.0)</td>
<td>0</td>
<td>0</td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 (2.0)</td>
<td>0</td>
<td>0</td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>1 (2.0)</td>
<td>0</td>
<td>1 (2.0)</td>
<td>2 (3.7)</td>
<td></td>
</tr>
<tr>
<td>Blister</td>
<td>1 (2.0)</td>
<td>0</td>
<td>0</td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Skin irritation</td>
<td>0</td>
<td>0</td>
<td>1 (2.0)</td>
<td>1 (1.9)</td>
<td></td>
</tr>
</tbody>
</table>

A subject could have had $\geq 1$ Preferred Terms reported under a given System Organ Class; AEs occurring during the washout period between treatments were attributed to the last treatment received before washout.
types of inhibitors due to other AEs; however, the effect of selumetinib on cardiac repolarization could still be minimal as the established PK/PD model demonstrated low potential for any QTc effects of selumetinib even at a supratherapeutic 150 mg dose.

CONCLUSIONS
A single 75 mg dose of selumetinib was not associated with QT/QTc interval prolongation in these healthy male subjects. The PK/PD model demonstrated the low potential for any QTc effects of selumetinib at a 150 mg single dose, which is twice the anticipated therapeutic dose. Therefore, selumetinib at the proposed therapeutic dose of 75 mg BID is unlikely to have a clinically relevant effect on cardiac repolarization in patients.

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CONFLICTS OF INTEREST
AstraZeneca contributed to the study design, collection, analysis, and interpretation of the data; writing of the manuscript; and the decision to submit the manuscript for publication.

Drs. Zhou, So, Huang, Holmes, Vik, Mariani, Zorenyi, and Al-Huniti are all full-time employees of AstraZeneca and hold stocks/shares in AstraZeneca. Dr. Martin and Mrs. Dymond are former employees of AstraZeneca and have stocks/shares in AstraZeneca. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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